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An Investigation of Formulation Factors and Processing Parameters for the Powder-Coating of Tablets

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An Investigation of Formulation Factors and Processing Parameters for the Powder-Coating of Tablets

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Dedication

To my parents.

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An Investigation of Formulation Factors and Processing Parameters for the Powder-Coating of Tablets

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Dry powder coating of pharmaceutical dosage forms has been investigated as an alternative method to commonly used liquid based coating techniques. Eudragit® L 100-55 and Eudragit® L 30 D-55 have been employed in enteric film coatings using aqueous dispersions, organic solutions and compression coating. However, the copolymer has not been investigated in dry powder coating applications.

Initially, formulation factors and processing parameters were investigated for the dry powder coating of chlorpheniramine maleate tablets using Eudragit® L 100-55 as the delayed release polymer. Powder coating was studied as a method to prevent the migration of an ionizable, highly water soluble model drug into the polymeric film during the coating process. Eudragit® L 100-55 was pre-plasticized with triethyl citrate (TEC) using hot-melt extrusion and subsequently ground into a fine powder. Polyethylene glycol 3350 (PEG 3350) was used as a primer and low melting coating excipient to

enhance coating powder adhesion and to improve film formation. The powder coating process was performed in a modified laboratory scale spheronizer.

For the dry-powder coating of sodium valproate tablets different subcoating materials were investigated to improve powder adhesion to the substrate and to reduce the level of Eudragit® L 100-55 required for gastric resistance. PEG 3350 and Methocel® K4M were incorporated in the Eudragit® E PO and Eudragit® RL PO subcoating formulations as pore forming materials. The miscibility of the PEG 3350 and Methocel® K4M in the film coating was correlated with their ability to function as pore forming agent.

The film formation process of thermally cured Eudragit® L 100-55 dry-powder coatings was characterized. The influence of film additives on relative melt viscosity, surface free energy of the polymer and the mechanical properties of powder-cast films was studied.

The influence of Eudragit® E PO in Eudragit® L 100-55 film coatings applied by a dry powder coating technique on the drug release mechanism was investigated. Calculation of the Flory-Huggins interaction parameter based on solubility parameters and different analytical techniques demonstrated immiscibility of the copolymers at processing conditions. A broad range of pH dependent theophylline release profiles were obtained as a function of the polymer blend ratio.

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Chapter 1: Introduction

1.1 DRY COATING OF PHARMACEUTICAL DOSAGE FORMS

1.1.1 Coating of pharmaceutical dosage forms

Dry coating of pharmaceutical dosage forms has been widely investigated as alternative to liquid based coating techniques. Sugar coating is a time-consuming process that is difficult to standardize and that requires highly skilled operators. Organic solvent based coating techniques are connected with environmental and safety related concerns. Other disadvantages include the relatively low polymer concentration of the coating formulation and from a toxicological standpoint, possible solvent residues in the final product. Aqueous coating has been widely used for the coating of pharmaceutical dosage forms. However, the process is not applicable for water-sensitive drugs. It has been reported that highly water-soluble drugs can migrate into the film coating, interfere with film formation and result in a premature drug release [1]. Another disadvantage is the slow drying rate. Usually slower spray rates and higher coating bed temperatures are used in aqueous coating compared to organic solvent based processes. Residual moisture was shown to affect the storage stability of the final product [2]. Water can cause hydrolysis reactions of active pharmaceutical ingredients and as plasticizer it may affect the permeability of the film coating. Bose and Bogner recently reviewed different solvent-free pharmaceutical coating techniques including compression coating, hot-melt coating, supercritical fluid coating, electrostatic spray powder coating, dry powder coating, and photocurable coatings [3].

1.1.2 Compression coating

The manufacturing process for compression coated dosage forms consists of two steps: compression of the core which is followed by a second compression of the outer layer around the core. The process is mainly used for the coating of tablets. Correct centering of the inner core is essential for a controlled drug release. Typical materials used for compression coating include polyethylene oxide, hydroxypropyl methylcellulose, carboxymethylcellulose, sodium alginate, and chitosan [3]. Upon contact with dissolution media or physiological liquids these materials forms a gel-like matrix. Erosion and diffusion of the swollen coating control the drug release rate. Important formulation considerations include the compactability of the outer layer material and bonding between core tablet and outer layer.

Mixtures of Eudragit® RS PO and Eudragit® S 100 were investigated for the compression coating of tablets to apply a seal coat onto constant-rate regulated release tablets [4]. The coating formulation consisted of granulated blends of Eudragit® RS PO (520g), Eudragit® S 100 (138g), triethyl citrate (35g), and magnesium stearate (7g). After curing of the compression coated tablets at 80ºC for 1 hour, the polymer coating was shown to be porous, allowing dissolution medium to enter the core tablet. NMR analysis was used to study the diffusion of water into the compression coated tablet.

Eudragit® L 100-55 was investigated alone or in combination with hydroxypropyl cellulose (HPC) and magnesium stearate for the compression coating of tablets containing nattokinase [5]. No additional plasticizer was listed in the manuscript. The coating was shown to prevent denaturation of the enzyme in gastric juice and the gastric

resistance was improved in the presence of HPC and reduced in combination with magnesium stearate.

One-Step Dry-Coating Technology (OSDrC®) is used to manufacture compression coated dosage forms in a single step [6, 7]. Rotary tableting machines with variable double-punch configuration were employed to coat Eudragit® L 100-55 onto core tablet containing either 5-fluorouracil or acetaminophen. The coating formulation contained Eudragit® L 100-55 (79%), magnesium aluminometasilicate (10%), triethyl citrate (10%), and magnesium stearate (0.6%) [6]. Prior to powder blending, the plasticizer triethyl citrate was adsorbed onto magnesium aluminometasilicate [6]. The tablets were not cured but stored at room temperature for 24 hours with desiccant prior to analysis. The compression coated tablets were acid resistant for 24 hours in No.1 fluid (pH 1.2) and thus complying with JP XIII. After 4 hours in No.1 fluid, the tablets were transferred to No.2 fluid (pH 6.8) and acetaminophen was rapidly released after approximately two more hours lag time [6]. The release of 5-fluorouracil was affected both in acid and buffer when Eudragit® L 100-55 was combined with chitosan [7]. Chitosan in Eudragit® L 100-55 compression coatings acted as pore forming agent in No.1 fluid. In No.2 fluid, chitosan delayed the release of 5-fluorouracil. The effect was dependent on the chitosan concentration.

1.1.3 Hot-melt coating

Lipids, waxes, polyethylene glycol are materials that have been investigated for the hot-melt coating of pharmaceutical dosage forms to obtain taste-masking or sustained

drug release. Recommended properties for the coating excipients encompass a melt viscosity of less than 300 centipoise and a melting point below 80ºC for flow and sprayability of the coating material [3] and is thus not used for Eudragit® polymers. One major stability concern of hot-melt coated dosage forms is the polymorphism of some employed coating excipients.

1.1.4 Supercritical fluid coating

Supercritical carbon dioxide can be used as solvent and anti-solvent in pharmaceutical coating applications. Supercritical fluid coating is mainly employed for the coating of drug particles. One formulation requirement is the insolubility of the core material in the supercritical fluid. Since most polymers have insufficient solubility in supercritical fluids, cosolvents are additionally used or the supercritical fluid is used as anti-solvent [3, 8]. Eudragit® RL 100 was investigated for the coating of silica nanoparticles employing an anti-solvent process [8]. Due to the limited solubility of the acrylic polymer in supercritical carbon dioxide, Eudragit® RL PO was dissolved in acetone. The spraying of the supercritical anti-solvent in the nanosuspension resulted in polymer nucleation on the silica nanoparticles. Since the process employed organic solvents, the process was not completely liquid free.

1.1.5 Photocurable coating

Photocurable coating technology is based on free-radical polymerization, initiated by UV or visible light and is hence not applicable for photosensitive drugs [3]. The coating formulation is based on liquid monomers, photoinitiator and/or photosensitizer. Bose and Bogner investigated siloxanes and methacrylates. The addition of pore formers such as sodium starch glycolate, lactose, and sodium chloride resulted in an increase in drug release rate. The toxicological profile of the coating excipients has not been established for all employed materials. Also possible chemical reactions with active pharmaceutical ingredients or core excipients have not been discussed.

1.1.6 Initiated chemical vapor deposition

Initiated chemical vapor deposition was investigated to apply methacrylic acid copolymers similar to Eudragit® L 100-55 onto silicon flats and three-dimensional particles [9]. The process involved free radical polymerization without any liquid or solvent phase. Adsorption of polymerized monomers from its vapor onto a cooled surface resulted in a polymer coating. *Tert*-butyl peroxide was used as radical initiator and methacrylic acid and ethyl acrylate as comonomers in different ratios. When ethylene dimethacrylate was used as alternate comonomer, the cross-linking agent *tert*-amyl peroxide was used as radical initiator. Ibuprofen microcrystals that were coated using initiated chemical vapor deposition did not possess sufficient gastric resistance. However,

silicon surfaces that were coated with methacrylic acid and ethylene dimethacrylate were stable at pH 1.2 and did not show any fluorescein release over 90 minutes.

1.1.7 Electrostatic spray powder coating

Electrostatic powder coating has been widely used in the metal finishing industry. Initially the coating powder particles are charged (potential difference to earth). The adhesion of the coating powder to a grounded substrate is followed by heat curing or IR radiation [3]. All used excipients must be characterized by some conductivity. Conductive properties can be obtained in pharmaceutical dosage forms with the use of materials possessing polar functional groups such as quaternary ammonium groups (i.e. cetrimide, benzalkonium chloride), by the incorporation of ionic salts, or high humidity treatment [3, 10]. Phoqus Pharmaceuticals, Ltd. developed scale-up and technology transfer strategies for the electrostatic dry powder deposition onto tablet cores [11]. However, there is little peer-reviewed literature on the technique. Electrostatic coating of pharmaceutical dosage forms with Eudragit® polymers, namely Eudragit® RS and Eudragit® E, have been claimed in several US patent applications [10, 12-15]. In addition to Eudragit® RS, the coating formulation may contain high molecular weight polyethylene glycol, polyethylene oxide, hydroxypropyl cellulose, xylitol, colorants and pigments such as aluminum lakes or titanium dioxide, disintegrants like sodium starch glycolate or croscarmellose sodium, wetting agents as sodium lauryl sulfate and glidants like colloidal silicon dioxide or glycerol monostearate [13]. The coating powder for electrostatic coating was obtained by wet granulation, followed by fluid bed drying and

micronization using a fluid energy mill. The mean particle size of the coating powder was approximately 10µm. Both sides of the tablet cores were coated separately using specialized equipment. Polymer particle fusion was completed with a curing step above 130ºC for 5 seconds employing IR radiation. Both Eudragit® RS and Eudragit® E formulation were also investigated to layer active pharmaceutical ingredients onto tablet cores using an electrostatic powder coating technique [15].

1.1.8 Dry powder coating

Thermosetting powder coatings have been investigated since the 1950s when for the first time powdered polyethylene was coated onto a preheated metal surface using a fluidized bed process [16]. In 1999 the first manuscript on the dry powder coating of oral pharmaceutical dosage forms was published by Obara et al. [17]. Hydroxypropyl methylcellulose acetate succinate (HPMCAS) was used as the enteric polymer with a particle size of not more than 10µm. The coating of pancreatin beads consisting of sugar seeds, corn starch, and low-substituted hydroxypropyl cellulose (L-HPC®) and placebo tablets containing spray-dried lactose, corn starch and L-HPC® was investigated in the study. The tablet cores were coated with hydroxypropyl methyl cellulose prior to application of the enteric polymer using an aqueous process to avoid penetration of the plasticizer into the core. Obara et al. used a centrifugal granulator for preliminary studies, a lab-scale ventilated pan coater, and a fluidized bed for the coating process. During the coating process, the exhaust air temperature which approximately corresponds to the bed temperature was kept at 42ºC and was increased to 50ºC during the curing phase.

HPMCAS was pre-blended with talc in a 10:3 ratio. The plasticizer triethyl citrate was combined with acetylated monoglycerides in a 3:2 ratio to reduce the necessary plasticizer level and increase coating efficiency. Acetylated monoglycerides demonstrated a low contact angle with HPMCAS which was directly correlated with an increased coating efficiency. The triethyl citrate level was 30% based on the dry polymer weight. Plasticizer dispersion and polymer powder were separately delivered into the coating bed, however powder feed and plasticizer spray started and ended simultaneously. As part of the curing process, an aqueous HPMC solution was applied onto the coated cores to increase the gastric stability, before the beads and tablets were dried with heated air until the exhaust temperature reached 50ºC. The aim of Obara's study was to shorten the processing time of coating processes by using a formulation with a higher polymer concentration. The final goal, to develop a completely liquid free process, was not achieved since water was still required during the curing phase to promote film formation [17]. Higher coating levels were required to ensure gastric resistance (25% polymer weight gain for dry coated beads compared to 18% for aqueous coating). However, the processing time was shortened to approximately one third compared to an aqueous coating process. Also physical stability of the dry coated tablets was comparable to ones prepared using an aqueous process after storage at 40ºC for 6 months. Both formulations showed a slight increase on disintegration time at pH 6.8.

Pearnchob et al. adapted the process that was developed by Obara et al. for Eudragit® RS PO and ethylcellulose [18, 19]. Prior to dry powder coating, the model drug propranolol HCl was layered onto nonpareils using hydroxypropyl methyl cellulose as binder and polyethylene glycol 4000 as plasticizer. Eudragit® RS PO was micronized,

obtaining a mean particle size of 9.4µm compared to 159.2µm of the bulk polymer. Talc was employed as glidant to improve flow of the polymer powder and was characterized with a mean particle size of 17.4µm. The polymer/talc mixture (1:1 w/w) was fed separately while the plasticizer was bottom-sprayed into a fluidized bed coater. The optimum plasticizer type and concentration was determined employing the minimum softening temperature. Different plasticizers were investigated for the coating with Eudragit® RS PO including triethyl citrate, acetyl tributyl citrate, as well as acetylated monoglycerides and each was combined with a 10% hydroxypropyl methyl cellulose aqueous solution to prevent agglomeration of the pellets. The fraction of plasticizer in the emulsion was 36.8 to 75.0% w/w. The optimum plasticizer level was determined to be 40% based on the polymer weight. More hydrophilic plasticizers such as triethyl citrate were shown to increase the drug release rate. Higher plasticizer levels generally decreased the drug release rate. The product temperature was kept between 34 and 36ºC during the coating process. Coating thicknesses between 50 and 100µm, corresponding to 9.9 and 19.6% weight gain, resulted in sustained release profiles. The Eudragit® RS PO coated pellets were oven-cured at 40ºC and 60ºC up to 24 hours to complete film formation and to avoid drug release rate changes over storage. The drug release rate did not change over three years of storage at room temperature when Eudragit® RS PO coated pellets were cured at 60ºC for two hours and acetylated monoglycerides was employed as plasticizer at a 40% level.

Similar studies were performed using ethylcellulose as extended release polymer with a D_v50 of 6.1µm [18]. The polymer/talc ratio was reduced to 10:3 for ethylcellulose. The amount of plasticizer in the emulsion with hydroxypropyl methyl cellulose aqueous

solution was between 50 to 75% w/w. Acetylated monoglycerides were shown to be the most effective plasticizer for ethylcellulose and to further reduce the drug release rate compared to triethyl citrate and acetyl tributyl citrate. The optimum plasticizer level was determined to be 40% w/w based on the polymer weight. Due to the high glass transition temperature of ethylcellulose of 130ºC, the product temperature was increased to 45 to 47ºC during the coating process. Following coating, the pellets were oven-cured at 60 or 80º for 2 or 24 hours. Curing at high humidity (100% RH) conditions accelerated film formation, resulted in a faster decrease in drug release, and may be employed to shorten curing times. Physical stability of the ethylcellulose dry powder coated pellets was confirmed over storage at room temperature over 3 years.

Pearnchob et al. also compared the dry powder coating process to conventional liquid-based coating techniques [20]. Besides Eudragit® RS PO and ethylcellulose, shellac was included in the study. Higher plasticizer concentrations, curing, and higher coating levels were generally required in dry powder coating processes compared to aqueous and organic solvent based coating techniques to obtain comparable drug release profiles as shown in Table 1.1. Similar coating levels required shorter processing times in dry powder coating applications such that total coating times were still shorter, although higher coating levels were necessary to control the drug release rate.

	Ethylcellulose			Eudragit® RS PO	
	Organic	**Aqueous**	**Dry powder**	**Aqueous**	**Dry powder**
Plasticizer	TEC	TEC	TEC	TEC	TEC
Plasticizer level	20%	25%	40%	20%	40%
Product temperature	29-31ºC	41-43ºC	45-47ºC	31-33ºC	34-36ºC
Coating level	5%	5%	20%	20%	20%
Coating time	111min	44min	30min	171min	41min

Table 1.1: Formulation and processing parameters for the coating of pellets with ethylcellulose and Eudragit® RS PO employing organic solvent based, aqueous, dry powder coating processes [20].

Kablitz et al. modified the process that was introduced by Obara et al. by using a three-way nozzle to deliver polymer and plasticizer dispersion jointly into the coating bed [21]. The coating process was performed in a rotary fluid bed. HPMCAS with a median particle size of 5.4µm was used as functional polymer. Talc was eliminated from the coating formulation since it was identified to disturb film formation. Colloidal silicon dioxide was used as an alternative anti-tack agent employing a concentration of approximately 1% based on the polymer weight. It was applied as overcoat after the coating process was completed. The coating efficiency increased when talc was replaced with colloidal silicon dioxide and when the plasticizer was combined with acetylated monoglycerides in a 7:3 ratio. An increased coating efficiency was directly correlated with an improved gastric resistance. A triethyl citrate concentration in the talc-free formulations of 23 to 24% based on the polymer weight resulted in a glass transition temperature of free films that were sprayed onto celluloid spheres of 42.5±0.6ºC. The coating process was performed at a product temperature of 40 to 42ºC [21]. During the

curing step the product temperature was raised to 53 to 55ºC. Curing of the dry coated pellets was demonstrated to be an essential step of the process. Drug release from uncured pellets followed zero order kinetics in acidic media and did not show an enteric release profile due to incomplete coalescence of the polymer particles. Approximately 50% of drug were released from uncured pellets after 2 hours in 0.1N hydrochloric acid. A 25% coating level and curing for 45 minutes provided the necessary gastric resistance. The drug release rate did not change after 6 months of storage; however, the storage conditions were not further specified in the publication.

The interparticle forces acting between HPMCAS and HPMCAS containing triethyl citrate and acetylated monoglycerides were determined using atomic force microscopy [22]. Acetylated monoglycerides was shown to be immiscible with HPMCAS using DSC and thus did not penetrate into the polymer. Since it remained on the surface, the adhesion force was shown to be highest between HPMCAS and acetylated monoglycerides containing formulations [22]. This effect was directly correlated to an increased coating efficiency. However, acetylated monoglycerides did not plasticize the polymer and did not promote film formation and was thus combined with triethyl citrate.

Kablitz et al. characterized the film forming process using scanning electron microscopy and dissolution studies using the same dry coating technique as described above [23]. To facilitate wetting of the pellets, the plasticizer dispersion was sprayed for 30 seconds onto the cores. The product temperature was kept at 25 to 26ºC to avoid premature film formation during the coating process. The pellets were then cured in an oven at temperatures up between 25 and 95ºC up to 24 hours. The glass transition

temperature of a film cast from an organic solution of the same formulation was characterized by a glass transition temperature of 51.7±3.3ºC. Different curing times and temperatures were investigated. As mentioned previously, polymer particle fusion occurs mainly during the curing phase of the coating process [21]. It was proposed, that prior to uptake into the polymer, the liquid plasticizer exerts capillary forces between the polymer particles [23]. During the curing phase, after absorption of the plasticizer into the polymer, viscous flow and particle deformation were anticipated to cause polymer particle sintering and coalescence. Curing at 55ºC for 45 minutes was determined to be the optimum curing conditions to obtain an enteric release profile since lower temperatures required longer curing times and higher temperatures caused sticking of the pellets. Kablitz et al. concluded that the glass transition temperature is the key parameter to determine the optimum curing conditions.

Cerea et al. and Zheng et al. developed a new dry coating technique for the coating of tablets [24, 25] in which the use of solvents or water was circumvented. Cerea et al. used Eudragit® E PO for taste masking and moisture protective coating of theophylline tablets [24]. Besides the model drug, the cores contained microcrystalline cellulose, lactose monohydrate, PVP K-30, magnesium stearate, and fumed silica. A laboratory scale spheronizer was modified for the dry coating process, employing a smooth stainless steel disc with 45º edges to ensure tumbling of the core tablets and avoid loss of coating powder. The optimum rotation speed was shown to be 190 rpm to facilitate tablet movement and prevent unnecessary friability of the tablet cores. The bed temperature was regulated using an infrared lamp as heat source and controlled using a digital temperature probe. The optimum bed temperature for the coating with Eudragit® E

PO was 55 to 60ºC. The glass transition temperature of Eudragit® E PO was determined to be 50±3ºC. Coating temperatures below 50ºC did not result in sufficient polymer adhesion whereas temperatures above 70ºC resulted in irregular polymer layering. The batch size was 50 g of tablets. Eudragit® E PO was pre-blended with 10% talc based on the polymer weight and fed onto the pre-heated tablet cores employing a single screw powder feeder at a rate of 0.5 g/min. Prior to coating, the coating powders were passed through a 100 mesh sieve. Curing of the coated tablets in a static oven on Teflon plates at 80ºC for 12 hours completed film formation. Optimum curing conditions were determined using free powder-cast films according to transparency of the film, film thickness, as well as surface and cross-sectional morphology using SEM analysis. Coating levels of 7 mg/cm^2, 10 mg/cm^2, and 14 mg/cm^2 of Eudragit® E PO resulted in a delay in drug release in pH 6.8 buffer. However no delay was occurring in pH 1.0 medium with more than 90% theophylline released after 30 minutes for the three investigated coating levels. The incorporation of hydrophilic polymers including Methocel® K4M, PVP K-90, glycerol monostearate, and polyethylene glycol 3350 in a 10% ratio based on the polymer weight decreased the lag time for drug release in buffer. In acidic medium only the addition of hydroxypropyl methyl cellulose was shown to reduce the drug release rate. The addition of low-melting coating excipients such as glycerol monostearate and polyethylene glycol were demonstrated to enhance coating powder adhesion.

Zheng et al. adapted the dry coating method developed by Cerea at al. as described above [25]. The process was modified for the acrylic polymers Eudragit® RS and RL PO for sustained release film coatings. The original process consisted of three

steps: pre-heating of the tablets, powder layering, and curing. The modified method for Eudragit® RS and RL PO, in contrast, required pre-plasticization of the polymer and priming of the pre-heated tablets to improve coating powder adhesion. Eudragit® RS/RL in a ratio of 95:5 was pre-plasticized with 5 to 15% triethyl citrate based on the polymer weight using hot-melt extrusion to avoid the separate spraying of the plasticizer. Following extrusion, the polymer was cut into pellets and ground into a fine powder, using a cryogenic process. The processed Eudragit® RS/RL PO was mixed with talc in a 10% ratio based on the weight of the polymer and directly fed onto the core tablets. The same equipment was used as by Cerea et al. and also the feeding rate of the coating powder was kept at 0.5 g/min. The coating bed temperature varied according to the plasticizer level between 55 to 60 for 15% triethyl citrate and 80 to 85ºC for 0% triethyl citrate. Similarly, curing was performed in a static oven at 80ºC, however, the curing time was increased to 24 hours for complete film formation of Eudragit® RS/RL PO films. The D_v50 of the processed polymers with different plasticizer levels was 65 to 71μm. Smaller particles were demonstrated to accelerate polymer particle coalescence. A 3% weight gain cetyl alcohol primer that formed a molten layer on the core tablets was shown to modify the hydrophobicity of the tablet surfaces. Improved wetting of the core tablets for Eudragit® RS/RL resulted in an increase coating powder adhesion. The theophylline tablet cores were composed of model drug, microcrystalline cellulose, lactose monohydrate, PVP K-30, magnesium stearate, and fumed silica. The drug release rate from theophylline tablets dry coated with pre-plasticized Eudragit® RS/RL PO was shown to be dependent on curing temperature, curing time, plasticizer level, coating level, and particle size of the ground polymer. A polymer weight gain of 8% resulted in a

sustained release profile with a lag time of about 2 hours and approximately 70% theophylline were released after 12 hours. Physical stability of the dry coated tablets was confirmed in closed HDPE containers at 25ºC/60%RH and 40ºC/75%RH over a period of 3 months.

1.2 PRINCIPLES OF COATING POWDER ADHESION

Sufficient powder particle adhesion is essential in dry-coating processes. True contact between two surfaces can only occur for ideally smooth surfaces since surface roughness acts as adhesion barrier [26]. The deformation of surface asperities improves the contact between surfaces. The Johnson, Kendall, Roberts theory (JKR theory) is used to determine the contact area between two atomically smooth spheres that are pressed into contact [27]. The diameter of the area is a function of external force, surface attractions, and elastic properties of the deformed particles [28].

Kendall distinguished different principles of adhesion by the range of action of adhesion force as two spheres are separated [26]: molecular adhesion, electrostatic adhesion, liquid drop adhesion and suction pad. Molecular adhesion force falls off in nanometer range. Electrostatic adhesion reduces with the square of the separation distance from the centers of the two spheres. Both liquid drop and suction pad are characterized by a long-range action of the adhesive forces. In the suction pad model the atmospheric pressure holds surfaces together, which stays constant when the surfaces are separated. The similar mechanism applies to the liquid bridge adhesion model.

The Laplace pressure in the interpenetrating liquid acts on the surfaces of two particles, pulling them together [29]. Liquid bridges fill gaps between the particles and reduce the surface roughness of the particles such that capillary attraction, surface tension and viscous resistance of the liquid inhibit rapid separation [30, 31]. Rough surfaces result in insufficient atomic contact. A liquid bridge increases the attractive force due to capillary pressure although it results in a decrease of solid/solid molecular adhesion. A molten priming layer as used by Zheng et al. [25] may promote liquid bridge adhesion of the polymer particles in a powder coating process. Also the techniques as used by Obara and Pearnchob use the principle of liquid bridge adhesion by separate spraying of the plasticizer [17-20].

1.3 CHEMICAL STRUCTURE AND PROCESSING PARAMETERS OF EUDRAGIT® POLYMERS

1.3.1 Commercial forms of Eudragit® polymers

Eudragit® S 100, Eudragit® L100-55, Eudragit® RS PO, Eudragit® E PO and mixtures of pre-plasticized Eudragit® RS and RL PO have been studied in dry coating applications. Eudragit® polymers have been widely used as aqueous and organic solvent based coating for pharmaceutical dosage forms and as matrix materials in wet-granulation, spray-drying, and hot-melt extrusion processes. Dosage forms based on Eudragit® polymers have been widely investigated for oral, buccal, sublingual, transdermal, rectal, and vaginal applications.

Eudragit® polymers are copolymers based on acrylate and methacrylate and their esters. They are commercially available as organic solutions E 12.5, L 12.5, and S 12.5; as aqueous dispersions including L 30 D-55, FS 30 D, NE 30 D, NE 40 D, NM 30 D and RL/RS 30 D; as granules like RS 100, RL 100, and E 100; or as powder such as L 100-55, L 100, S 100, RS PO, RL PO, E PO [32]. Most of the Eudragit® polymers are listed in the European Pharmacopoeia, the United States Pharmacopoeia and the National Formulary, as well as the Japanese Pharmacopoeia.

1.3.2 Chemistry of Eudragit® polymers

Since the backbone of Eudragit® polymers is formed by carbon atoms it is stable in the presence of water, oxygen, light, digestive enzymes, and body fluids [33]. Eudragit® polymers are not metabolized and absorbed in the digestive tract [34]. The methyl pendant group of the methacrylate additionally stabilizes the molecule, resulting in a more rigid and brittle polymer, while the polymerization of acrylic monomers produce more flexible materials [33]. The methyl side group also increases the hydrophobicity of the polymer, as present in Eudragit® E polymers. Due to the methyl group, methacrylic acid is a weaker acid (pKa 4.66) compared to acrylic acid (pKa 4.25) [33].

After treatment with dilute acids or bases over 6 weeks, hydrolysis of less than 0.3% of the ester groups in polymethacrylic esters has been reported [35]. Ester groups in acrylic ester copolymers are more likely subject to hydrolysis. As powder or granular form, Eudragit® polymers did not show a loss of functional groups after storage for up to

5 years [2]. Side chain degradation of Eudragit® polymers was shown to occur above 150ºC, depolymerization and cross-linking of the main chain above 180ºC [2]. Neutral and anionic copolymers were demonstrated to be more heat-stable that cationic ones.

The melt viscosity of Eudragit® polymers is dependent on the molecular weight and the amount of methacrylic acid in the molecule. High methacrylic acid contents were shown to increase while high concentrations of acrylic esters were demonstrated to decrease the melt viscosity of Eudragit® polymers [33].

1.3.2.1 Eudragit® L 100, S100, FS 30 D, L 30 D-55, and L 100-55

Eudragit® L, S, and FS polymers are gastroresistant and enterosoluble methacrylic copolymers with free carboxylic acid groups. Eudragit® L 30 D-55 and Eudragit® L 100-55 are based on methacrylic acid and ethyl acrylate in a 1:1 ratio, soluble above pH 5.5 and thus used for the delivery of drugs to the upper small intestine. The average molecular weight is approximately 250,000 [32]. The commercial product contains additionally 0.7% sodium lauryl sulfate and 2.3% polysorbate 80 based on solid substances. Eudragit® L and S contain methacrylic acid and methyl methacrylate. Since Eudragit® L contains higher amounts of methacrylic acid (approximately 50:50 compared to approximately 30:70 for Eudragit® S) it is soluble above pH 6.0 while Eudragit® S starts to dissolve above pH 7.0. The average molecular weight of Eudragit® L and S is approximately 135,000 [32]. Eudragit® FS 30 D is based on methacrylic acid, methyl acrylate as well as methyl methacrylate and is soluble above pH 7.0. The fraction of free carboxyl groups to ester groups is about 1:10. The average molecular weight is

approximately 220,000. Combinations of Eudragit® S and L 100 [34] and Eudragit® FS 30 D can be used for pH dependent colonic delivery.

Not only the amount of free carboxylic groups influences the pH-dependent solubility of Eudragit® L, S, FS and L 55. The exchange of methyl methacrylate as present in Eudragit® L 100 with ethyl acrylate as in Eudragit® L 100-55 results in a decrease of the dissolution pH. The dissolution is also dependent on the pKa value of the acid component and on the ionic strength of the dissolution media and is accelerated in the presence of divalent and trivalent ions such as phosphate and citrate [33]. Dissociation of the salts at the interface between enteric coating and core due to water penetration through the enteric coating may affect the microenvironmental pH. As a result, active pharmaceutical ingredients or excipients based on a strong acid and a weak base can improve the gastric resistance of enteric coated dosage forms and may delay the release in buffer whereas salts composed of a weak acid and a strong base may decrease the stability of the enteric coating in gastric fluid [33]. Non-ionic subcoatings were recommended to prevent this phenomenon [33].

1.3.2.2 Eudragit® E PO, E 100, and E 12.5

Eudragit® E is a cationic copolymer composed of dimethylaminoethyl methacrylate and neutral methacrylic esters in a 1:1 ratio. The average molecular weight is approximately 150,000 [32]. The tertiary amino group in Eudragit® E makes the polymer gastrosoluble and applicable for taste masking. The polymer is soluble below pH 5 due to salt formation of the tertiary amino group of Eudragit® E, which is present in a

high quantity in the polymer [34]. Above pH 5 Eudragit® E polymers absorb water and swell due to the presence of the hydrophilic amino groups causing disintegration of the coating even at high pH [34].

Eudragit® E films are characterized by very low water permeability compared to Eudragit® RL PO and hydroxypropyl methyl cellulose coatings and are thus employed as moisture protective coatings. The addition of hydrophilic excipients including polyethylene glycol, lactose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, and microcrystalline cellulose were recommended to increase the permeability of Eudragit® E film coatings [32].

1.3.2.3 Eudragit® NE 30D/40D and Eudragit® NM 30 D

The neutral methyl and butyl esters of Eudragit® NE and NM polymers result in insoluble, permeable (pH independent) formulations. The average molecular weight of Eudragit® NE is approximately 800,000. Due to its high flexibility, Eudragit® NE 30 D does not require the addition of plasticizer. The average molecular weight of Eudragit® NM 30 D is approximately 600,000 [32].

1.3.2.4 Eudragit® RS/RL PO, RS/RL 100, and RS/RL 30 D

Eudragit® RL and RS polymers are insoluble, swellable, and permeable (pH independent) polymers due to trimethylammonioethyl methacrylate functional groups. The average molecular weight is approximately 150,000 [32]. The quarternary

ammonium groups in Eudragit® RL and RS increase the hydrophilicity and permeability of the polymer. The molar fraction of the quaternary ammonium groups to neutral methacrylic acid ester groups is 1:20 (approximately 50 mEq/100g) for Eudragit® RL and 1:40 (approximately 25 mEq/100g) for Eudragit® RS and influence the swellability as well as permeability of the polymers. The water permeability of Eudragit® RL is approximately twice as high as the permeability of Eudragit® RS PO [33]. The ratio of RL and RS, which are miscible in all ratios, can be modified to adjust the drug release profile [34, 36]. Thin Eudragit® RL coatings (10 – 30 μm) were also recommended as fast-disintegrating protective coatings due to a high diffusion rate of dissolved drug through the film [37]. Diffusion through Eudragit® RS films was reduced compared to Eudragit® RL films and was dependent on molecular size of the drug and steric effects. The diffusion rate of phenyl propanolamine was about 8 times fold increased through a RL membrane (approximate thickness 25 μm) compared to an RS membrane [37]. The factor was 3 for chlorpheniramine maleate using the same experimental set-up.

Penetration of dissolution medium into the core followed by diffusion of dissolved drug through pores into the surroundings was proposed as drug release mechanism from dosage forms that were coated with Eudragit® RL/RS mixtures [38]. The pores in Eudragit® RL films were shown to be larger than in Eudragit® RS films. The release from dosage forms that were formulated with Eudragit® RL and RS is pH independent due to ionization of the quarternary ammonium group at all pH levels occurring in the digestive tract [36]. However, the drug release was shown to be dependent on ionic strength and buffer species of the dissolution medium [36, 39, 40].

1.3.3 Formulation and processing parameters for Eudragit® polymers

The addition of plasticizers reduces the glass transition and minimum film-formation temperature of hard and brittle Eudragit® polymers to prevent cracking and splitting of the film coating [2, 41]. Most commonly used are triethyl citrate, triacetin, propylene glycol, and polyethylene glycol [37]. More hydrophobic plasticizers include tributyl citrate, dibutyl phthalate, and tertiary butyl acetate. The usual plasticizer level for aqueous coating applications is 10 to 20% based on the dry polymer weight [33, 37]. Higher levels of 40 to 50% of triethyl citrate may be required for Eudragit® L100 and S 100 [41].

Talc, magnesium stearate, and glycerol monostearate have been used to reduce the tackiness of the film coating during processing. Talc was also shown to improve the smoothness of the film coating [37]. A talc content of 25% based on the weight of the dry polymer weight was sufficient in aqueous coating applications. The addition of 50% talc resulted in opaque film coatings, however, the spray rate may be increased [37]. Glycerol monostearate was usually used in a concentration of 2 to 15%.

Several hydrophilic and hydrophobic film additives including sucrose, lactose, microcrystalline cellulose, poly (vinyl pyrrolidone), poly (vinyl alcohol), and polyethylene glycol have been investigated to modify the drug release rate from dosage forms that were coated with Eudragit® polymers [33, 35, 36].

Eudragit® L 100 and Eudragit® L 100-55 were shown to have an ion exchange capacity of approximately 6 mEq/g. The ion exchange capacity of Eudragit® S 100 was determined to be approximately 3.5 mEq/g [37]. Drugs may adsorb to the polymer, but

will be eluted upon contact with digestive fluids. Acids like salicylic acid were shown to adsorb to Eudragit® RL/RS in water or alkaline media [42]. Also Eudragit® E 100 was shown to interact with anionic drug as ibuprofen after repeated heating [2].

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Chapter 2: Research Outline

2.1 OVERALL OBJECTIVE

The overall objective was to develop a powder coating process using Eudragit® L 100-55 for the coating of tablets, to investigate formulation factors, and processing parameters on product performance and to characterize the film forming mechanisms. Eudragit® L 100-55, an anionic acrylic copolymer, has been studied for the compression coating of tablets as well as aqueous and organic solvent based film coating of pharmaceutical dosage forms. However, it has not been investigated for dry powder coating applications. The coating process itself is based on a water and solvent-free technique that was developed by Cerea and Zheng et al. in 2004 to circumvent limitations of the established aqueous and organic coating systems for pharmaceutical products [1, 2]. The dry powder coating process was successfully employed for the acrylic polymers Eudragit® RS/RL PO and Eudragit® E PO for the coating of tablets. The powder coating process consisted of three steps, namely priming, powder layering and curing. To avoid the separate spraying of the plasticizer, polymers with a high glass transition temperature were pre-plasticized using a hot-melt extrusion process and subsequently ground into a fine coating powder using a cryogenic process.

2.2 SUPPORTING OBJECTIVES

2.2.1 Investigation of the Influence of Processing Parameters and Formulation Factors on the Drug Release from Tablets Powder-coated with Eudragit® L 100-55

Migration of active pharmaceutical ingredients into the film coating has been reported for aqueous dispersion based coating applications [3]. In chapter 4, powder coating technology was investigated as a method to prevent the migration of the ionizable, highly water soluble drug chlorpheniramine maleate (CPM) into the film coating. Formulation factors such as plasticizer level and coating additives were investigated and the optimum processing parameters including coating and curing conditions were determined. The coating powder characteristics as well as interactions between film components and the active ingredient were investigated using differential scanning calorimetry (DSC). The drug release properties as well as the physical stability of the coated tablets during storage at accelerated conditions were studied using dissolution and high performance liquid chromatography (HPLC).

2.2.2 Investigate the Influence of Polymeric Subcoats on the Drug Release Properties of Tablets Powder-coated with Pre-plasticized Eudragit® L 100-55

The coating of sodium valproate tablets with Eudragit® L 100-55 employing dry-powder coating technology was investigated in chapter 5. Sodium valproate is a hygroscopic drug and affects the microenvironmental pH of the hydrated core during

dissolution [4]. The influence of polymeric subcoats on the release of sodium valproate from tablets that were powder coated with pre-plasticized Eudragit® L 100-55 was studied using dissolution testing and HPLC. Since both Eudragit® RL PO and Eudragit® E PO are insoluble at pH 6.8 and delay the drug release during the buffer stage of the USP enteric test, pore forming agents were added to the subcoating formulation. The miscibility of pore forming agents in the functional polymers and the effect of the incorporation into the subcoat on the drug release rate were investigated using dissolution testing, HPLC and DSC. Interfacial interactions between tablet surface and coating powder are complex and were shown to be dependent on interfacial tension, wetting and adhesion [5]. Wetting properties and spreading of the primer polyethylene glycol 3350 (PEG 3350) over the tablet cores were investigated using solubility parameters.

2.2.3 Study of the Influence of Additives on Melt Viscosity, Surface Tension, and Film Formation of Dry Powder Coatings

The main factors that determine polymer particle fusion and leveling of a polymeric film that was applied using a dry coating technique are surface tension and melt viscosity of the polymer [6, 7]. In chapter 6, both parameters were determined for Eudragit® L 100-55. Since the incorporation of coating excipients was shown to affect both melt viscosity and surface tension, the influence of additives on both parameters and on film formation of Eudragit® L 100-55 coatings was studied. Mechanical testing was used to evaluate puncture strength and elongation of free powder-cast films as a function of progress in film formation.

2.2.4 Characterize the Properties of Theophylline Tablets Dry Powder Coated with Eudragit® E PO and Eudragit® L 100-55

In chapter 7, the influence of Eudragit® E PO in Eudragit® L 100-55 film coatings applied by a dry powder coating technique on the drug release mechanism of theophylline from tablets was analyzed. Due to the different pH-dependent solubility properties of the polymers, complexes of both materials were used in sustained release dosage forms [8]. Physical blends and micronized extrudates of different polymer ratios were investigated for the powder-coating of theophylline tablets employing dissolution testing and UV analysis. The miscibility of the two polymers was studied and interactions were characterized using DSC, Fourier transform infrared spectroscopy (FT-IR), and scanning electron microscopy (SEM).

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Chapter 3: Materials and Methods

3.1 MATERIALS

Eudragit® L 100-55, Eudragit® RL PO, and Eudragit® E PO were donated by Evonik Industries AG (Piscataway, NJ). Chlorpheniramine maleate USP (CPM), sodium valproate, anhydrous theophylline USP, lactose monohydrate NF, and magnesium stearate NF were purchased from Spectrum Chemical Mfg. Corp. (Gardena, CA). Triethyl citrate NF (TEC) was donated by Vertellus Materials Inc. (Greensboro, NC). Talc USP (Imperial 500) was supplied by Luzenac America, Inc. (Centennial, CO). Polyethylene glycol (PEG) 3350 NF and hydroxypropyl methylcellulose (Methocel® K4M) were obtained from The Dow Chemical Company (Midland, MI). Microcrystalline cellulose (MCC, Avicel® PH-200 and PH-101) was donated by FMC BioPolymer (Newark, DE). Polyvinylpyrrolidone K-30 (PVP, Kollidon® 30) was supplied by BASF Corp. (Mt. Olive, NJ). Colloidal silicon dioxide (Cab-O-Sil® M-5P) was donated by Cabot Corporation (Billerica, MA).

3.2 METHODS

3.2.1 Coating powder preparation

Eudragit® L 100-55 and Eudragit® RL PO were pre-plasticized using a method reported by Zheng et al. [1] for the pre-plasticization of Eudragit® RS / RL PO blends. Polymer and different concentrations of the plasticizer triethyl citrate (TEC) were mixed using a high shear mixer. The powder blend was hot-melt extruded employing a single screw extruder (Randcastle Model RC 0750, Cedar Grove, NJ) using a cylindrical die with an inner diameter of 6mm. For the extrusion of Eudragit® L 100-55, the temperature zones were set to: zone 1 = 80ºC, zone 2 = 110ºC, zone 3 = 115ºC, and die = 120ºC and for Eudragit® RL PO to: zone 1 = 80ºC, zone 2 = 105ºC, zone 3 = 115ºC, and die = 125ºC. Different ratios of Eudragit® E PO and Eudragit® L 100-55 that contained 30% TEC based on the weight of the enteric polymer were extruded at the following temperatures: zone 1 = 65ºC, zone 2 = 110ºC, zone 3 = 115ºC, and die = 120ºC. The extrudate was subsequently cut into pellets with a Randcastle RCP-2.0 pelletizer and then cryogenically ground into a fine powder using a CF Mikro-Bantam Cryogenic Grinder (Micron Powder Systems, Summit, NJ). To obtain a more uniform particle size distribution and exclude fines and large particles, the ground pre-plasticized polymer was sieved by mechanical shaking for 15 minutes. The particle size fraction between 100 and 200 mesh (75 - 150μm) was used for the dry powder coating experiments.

3.2.2 Tablet preparation and characterization

The API such as chlorpheniramine maleate (CPM), theophylline, or sodium valproate, fillers including microcrystalline cellulose, lactose monohydrate NF, and the binder Kollidon® K 30 were mixed in a V-shape blender (Model Yoke, Patterson-Kelley Co., East Stroudsburg, PA) or a low shear mixer for 15 minutes. Following the addition of the magnesium stearate and colloidal silicon dioxide, the mixture was blended for an additional 5 minutes. The tablets were compressed either on a rotary press (Model FJS-B2 Stokes, Bristol, PA) or a single stage press (Stokes F press, Bristol, PA) using deep concave 5 mm punches. The tablet hardness was measured using a hardness tester (WTP-3, Heberlein &. Co. AG, Wattwil, Switzerland). The disintegration time was determined according to USP 29 using a USP Disintegration Tester (Vankel Industries Inc., Chatham, NJ). The tablet friability was tested according to USP 29 with a Tablet Friability Apparatus (Vankel Industries Inc., Chatham, NJ).

3.2.3 Powder coating process

Powder coating of the tablets was performed according to the method reported by Cerea et al. (2004) and Zheng et al. (2004) in a modified laboratory scale spheronizer (Model 120, G.B. Caleva, Dorset, UK) [1, 2]. The batch size was 40 g of tablets. The rotation speed of the spheronizer was adjusted for each coating formulation and varied between 170 and 220 rpm. The coating bed temperature was dependent on formulation and the plasticizer content of the coating powder and maintained between 65 and 75ºC.

The temperature of the coating bed was monitored by measuring the surface temperature of the tablets using a Fluke 61 Infrared Thermometer (Fluke Corporation, Everett, WA). Some formulations required the addition of the anti-tack agent talc and the low-melting coating excipient polyethylene glycol 3350 (PEG 3350). The feeding rate of the coating powder onto the tablets cores was dependent on the capacity of the coating powder to adhere, which decreased with increasing coating levels. Following the application of the priming layer of molten PEG 3350, the polymer mixture was fed onto the tablet surfaces at a feeding rate of about 3 g/min until a polymer weight gain of 7% to 10% was obtained. The powder-feeding rate was then reduced to 0.5 g/min. Since all coating formulations exhibited poor flow properties, the powder mixtures were manually fed onto the tablet surfaces. After completion of the coating process, the tablets were subsequently cured either in the operating spheronizer for or in a static oven on Teflon trays at different temperatures for varying times

3.2.4 Drug release study

Dissolution testing was performed using the USP 29 or USP 30 Apparatus 2 (Vankel VK 6010; Vankel Industries Inc., Cary, NC). The dissolution media were maintained at 37 °C and agitated at 50 rpm. Samples were withdrawn by an autosampler (Vankel VK 8000; Vankel Industries Inc., Cary, NC). The drug release rate of the model drugs from powder-coated tablets was investigated using different dissolution media. A modified USP 29 Drug Release Standard for Enteric-Coated Articles, Method B was employed by placing coated tablets initially in 900 mL 0.1N HCl for two hours, followed

by 4 hours in 900 mL pH 6.8, 50 mM phosphate buffer. Furthermore, the USP Drug Release Standard for Enteric Coated Articles, Method A was used to characterize the release properties of the coated tablets. Following two hours dissolution in 750 mL, 0.1N HCl, 250 mL of 0.2M tribasic sodium phosphate solution were added to the dissolution vessel to adjust the pH of the dissolution medium to 6.8 ± 0.05. The drug release study was then resumed for 2 more hours. Alternatively, *in vitro* dissolution testing was conducted to investigate the theophylline release rate from powder-coated tablets in either 900 mL of 0.1N HCl or in 900 mL pH 6.8, 50 mM phosphate buffer for 12 hours.

3.2.5 HPLC analysis

The plasticizer content in the extrudates and free films as well as the concentration of the model drug in the dissolution medium were determined using a Waters high performance liquid chromatography (HPLC) system (Waters, Milford, MA) equipped with a photodiode array detector (Model 996). Prior to analysis, all samples were filtered using 0.2μm or 0.45μm nylon filters. The samples were injected by an autosampler (Model 717plus), and Empower® Version 5.0 software was used to collect and analyze the data.

The TEC content was analyzed at a wavelength of 210 nm using an ODS-3 3μm, 150mm × 4.6mm column (Alltech Inertsil™, Deerfield, IL, USA) at a column temperature of 30 ± 2ºC. Prior to HPLC analysis, processed polymer or powder cast film samples were initially dissolved in 50 mM pH 7.4 buffer and then 1:2 diluted with 50mM pH 2.5 phosphate buffer to precipitate the polymer from the solution. The injection

volume was 50 µL. The mobile phase contained a mixture of acetonitrile and pH 2.5 10 mM phosphate buffer in volume ratios of 55:45. The flow rate of 1 mL/min resulted in a retention time of 4.0 min for TEC. Linearity was demonstrated in the concentration range of 100 to 500 µg/mL ($R^2 > 0.999$).

An ODS-3 3 µm, 150 mm × 4.6 mm column (Alltech Inertsil™, Deerfield, IL, USA) was used to detect CPM at a wavelength of 260 nm. The column temperature was maintained at 40 ± 2ºC. The injection volume was 50 µL. The mobile phase contained a mixture of water:methanol:triethylamine in volume ratios of 675:325:4.5. The retention time of CPM was 9.5 min at a flow rate of 1mL/min. Linearity was demonstrated from 2 to 50 µg/mL ($R^2 > 0.999$).

The injection volume for theophylline was 40 µL. The mobile phase consisted of water:acetonitrile:glacial acid in volume ratios 845:150:5 and 1.156 g/L of sodium acetate trihydrate. The flow rate was 1 mL/min, and the retention time of theophylline was 4 minutes. Linearity was confirmed from 1 to 60 µg/mL ($R^2 > 0.999$).

A wavelength of 210 nm was employed to analyze the sodium valproate concentration in the dissolution samples. A Phenomenex Luna C18(2), 3 µm, 150 mm × 4.6 mm column (Phenomenex Inc., Torrance, CA) was used at a column temperature of 30 ± 2ºC. The injection volume was 50 µL. The mobile phase contained a mixture of sodium phosphate monobasic and acetonitrile in a volume ratio of 63:37. The pH of the mobile phase was adjusted to 2.3 using phosphoric acid. A flow rate of 1 mL/min resulted in a retention time of 18 min for sodium valproate. Linearity was demonstrated from 4 to 100 µg/mL ($R^2 > 0.999$).

3.2.6 UV analysis

UV Analysis was conducted to analyze dissolution samples for theophylline content using a μQuant (Bio-Tek® Instruments Inc., Winooski, Vermont) at the detection wavelength 278 nm. Prior to analysis, the samples were filtered using 0.45 μm nylon filters and diluted with an equal volume of dissolution medium. Linearity was demonstrated from 1 to 25 μg/mL (R^2 > 0.999). SPSS Version 15.0 was used to statistically analyze the dissolution results.

3.2.7 Particle size analysis

Laser light diffraction was used to analyze the particle size distribution of the coating powders with a Malvern Mastersizer S (Malvern Instrument Limited, Malvern, Worcestershire, UK). D_v 10, D_v 50, and D_v 90, the cumulative percent undersize, were determined using the diffractive index of Eudragit® L 100-55 (n_D^{20} = 1.3899) and the approximate diffractive index of Eudragit® E PO (n_D^{20} = 1.3899) in purified water (n_D^{20} = 1.3300).

3.2.8 Residual moisture analysis

A MF-50 Moisture Analyzer (A&D Engineering, Inc., Milpitas, CA) was employed to determine the loss on drying of the coating powder. A sample of 2 g was

dried to a constant weight, as defined by a weight change of less than 0.05% per minute at 110ºC.

3.2.9 Contact angle measurements

Sample compacts were prepared at a 500kg or 1000kg compression force using a Carver Laboratory Press (Model M, ISI Inc., Round Rock, TX). 3 μL of water, ethylene glycol or diiodomethane were placed onto the surface of the compacts with a microsyringe. The contact angle was determined by measuring the tangent to the curve of the sessile droplet using a Goniometer (Model No. 100-00-115, Ramé-Hart Inc., Mountain Lakes, NJ) within 5 seconds after drop deposition. The measurements were performed in a series of 3 samples.

3.2.10 Film preparation

Free films were prepared from different coating powder formulations using Teflon coated aluminum dishes with a Teflon coated lid. The powder was either powder-cast or compressed into films using a compression force of 10 kN on 22 cm^2 of film for 3 minutes (Carver Laboratory Press, Model M, ISI Inc., Round Rock, TX). All samples were subsequently cured in a static oven at 60ºC at a reduced compression force of approximately 10 N.

Film samples of 3x3 mm were immersed in 15 mL of 0.1N HCl and shaken at 100 rpm at 37ºC for 2 hours using a Lab-Line® Orbit Environ-Shaker (Lab-Line Inctruments

Inc., Melrose Park, IL). A volume of 5 mL 0.2M tribasic sodium phosphate solution was added to adjust the pH of the dissolution medium to 6.8 ± 0.05 and the film dissolution was continued for 2 more hours.

3.2.11 Mechanical testing

Mechanical testing of powder-cast films was performed using a puncture test that was adapted from a method previously described by Bodmeier et al. [3]. A Chatillon Universal Tension / Compression Tester Model TCD-200 (Ametek, Largo, FL) was employed with a DFGS 50 digital force gauge to analyze puncture strength and elongation of powder-cast films. Prior to analysis, the film specimen was mounted onto the open mouth of a film holder that consisted of an aluminum cup with an inner diameter of 15 mm and an upper mounting plate. The puncture probe (length, 31 mm; diameter, 6 mm; dome shaped probe end) was lowered toward the center of the film specimen at a crosshead speed of 10 mm/min. The load and deflection at maximum were used to determine the maximum puncture strength and % elongation (puncture strength = F/A_{cs}, where F is the load and A_{cs} is the cross-sectional area in the path of the cylindrical opening; % elongation = $[\{(R^2 + D^2)^{1/2} – R\}/R]\cdot 100$, where R is the radius of the film and D is the deflection of the probe). SPSS Version 15.0 was used for the statistical analysis of the data.

3.2.12 Differential scanning calorimetry

To characterize the thermal properties of the melt extrudates and powder cast films, modulated differential scanning calorimetry (MDSC) was conducted using a Thermal Advantage Model 2920 (TA Instruments, New Castle, DE) equipped with Universal Analysis 2000 software. Ultrahigh pure nitrogen was used as the purge gas at a flow rate of 150 ml/min. Prior to analysis, the samples were sealed in aluminum pans (Kit 0219-0041, Perkin-Elmer Instruments, Norwalk, CT). The temperature ramp rate was either 3°C/min or 5°C/min at a modulation rate of ±1.00°C every 60 seconds. The reverse heat flow of the second heating cycle was used to determine the inflection glass transition temperature. Linear peak integration was used to determine the heat of fusion.

To study potential interactions between excipients and the model active pharmaceutical ingredients, conventional differential scanning calorimetry (DSC) was used employing the same instrument as described above. The samples were heated from 50ºC to 300ºC using a temperature ramp rate of 10ºC/min. The raw materials were analyzed as well as physical mixtures. The heat flow of the first heating cycle was used to determine the melting points and heat of fusion values.

3.2.13 Thermogravimetric analysis

The thermal stability of the coating excipients and a powder-cast film was investigated using thermogravimetric analysis (TGA). A sample of approximately 10 mg was equilibrated to 50ºC and then heated at a temperature ramp rate of 10ºC/min to

800ºC. At isothermal conditions, the equilibration of the sample to 50ºC was followed by heating to 60ºC and the temperature was then kept constant for 6 hours.

3.2.14 Relative melt viscosity

A Haake MiniLab-Compounder (Thermo-Fisher Scientifc Inc., Waltham, MA) was used in the cycle mode to determine the mixing torque for Eudragit® L 100-55 containing various amounts of TEC and PEG 3350. The screw speed was set to 10 rpm. The temperature range was adjusted for each formulation. The maximum temperature did not exceed 125ºC to avoid side chain degradation of the polymer [4]. The torque cut off value occurred at 550 Ncm.

3.2.15 Scanning electron microscopy

The morphology of the surface and cross-section of powder-cast films and coated tablets was analyzed by scanning electron microscopy (SEM) using either a Hitachi, Model S-4500 FE (Hitachi, London UK) operated at 10 kV and 20 mA or a LEO 1530 Gemini scanning electron microscope (Zeiss/LEO, Oberkochen, Germany) operated at 10 kV. The samples were sputter coated with either gold/palladium (60:40) using a Ladd Benchtop Sputter Coater (Ladd Research, Winston, VT) or with platinum/palladium (80:20) using a Cressington Sputter Coater 208 HR equipped with a Thickness Controller MTM 20 (Cressington Scientific Instruments Ltd., Watford, UK).

3.2.16 Fourier transform infrared spectroscopy

To characterize interactions occurring between model drugs and excipients, Fourier transform infrared spectroscopy was conducted using a Nicolet Magna IR-560 FT-IR spectrometer. Prior to analysis, the samples were compressed with potassium bromide into pellets under vacuum using a compression pressure of 10 tons.

3.2.17 ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy

^{1}H and ^{13}C nuclear magnetic resonance spectroscopy (^{1}H and ^{13}C NMR) was performed to investigate possible interactions between model drug and excipients. For NMR analysis, the sample was dissolved in deuterium dioxide containing 3-(trimethylsilyl)-propionic acid-D4, sodium salt (TSP) as the internal standard. The NMR spectra were obtained using a Varian Inova 500 (Varian Inc., Palo Alto, CA).

3.3 REFERENCES

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Chapter 4: Investigation of the Influence of Processing Parameters and Formulation Factors on the Drug Release from Tablets Powder-coated with Eudragit® L 100-55[1]

Abstract:

The aim of this study was to develop a dry powder coating process for chlorpheniramine maleate (CPM) tablets using Eudragit® L 100-55 as the delayed release polymer. Powder coating, a water and organic solvent-free process, was investigated as a method to prevent the migration of an ionizable, highly water soluble model drug into the polymeric film during the coating process. Eudragit® L 100-55 was pre-plasticized with triethyl citrate (TEC) using hot-melt extrusion at levels of 20, 30, and 40%, based on the polymer weight. The extrudate was subsequently cut into pellets and cryogenically ground into a fine powder. Talc was incorporated into the coating powder as an anti-tack agent. PEG 3350 was used as a primer for the powder coating of tablets with pre-plasticized Eudragit® L 100-55. The addition of polyethylene glycol 3350 (PEG 3350) to the pre-plasticized Eudragit® L 100-55 was necessary to enhance the adhesion of the coating powder to the tablet cores. PEG 3350 also improved film formation and coalescence of the polymeric particles due to its plasticization effects on the acrylic polymer. For comparison, theophylline tablets were also coated with pre-plasticized Eudragit® L 100-55. Theophylline was selected as a less water soluble model drug. The powder coating process was performed in a modified laboratory scale spheronizer. The

[1] Significant portions of this chapter were taken from: Sauer, D., W. Zheng, L.B. Coots, and J.W. McGinity, Influence of processing parameters and formulation factors on the drug release from tablets powder-coated with Eudragit L 100-55. European Journal of Pharmaceutics and Biopharmaceutics, 2007. 67: p. 464-475.

drug release rate was dependent both on TEC content and the coating level. The stability of the powder-coated CPM tablets was confirmed at 25ºC/60% RH over a storage time of 12 weeks.

4.1 INTRODUCTION

Although widely employed in other industrial applications since the 1950s, dry powder coating was not described in the pharmaceutical literature until the late 1990s. The primary advantage of this process is that it circumvents many limitations of established organic and aqueous coating systems for pharmaceutical products. The traditional use of organic solvents in coating processes creates environmental, toxicological, and safety-related concerns. Problems of aqueous coating are primarily due to the limited applicability for water-sensitive active ingredients [1], the migration of drugs into the polymer coatings during processing [2], and the physical aging of the polymeric films that leads to changes in the drug release rate during product storage [3-5].

The first approach to powder-coat pharmaceutical dosage forms was reported by Obara and coworkers in 1999 [6]. The process involved the direct application of polymeric particles and the simultaneous spraying of a mixture of a plasticizer and acetylated monoglyceride onto drug containing cores. An aqueous hydroxypropyl methylcellulose (HPMC) solution was applied during the curing step to improve film

formation [6]. Pearnchob et al. modified the technique using an aqueous HPMC solution in combination with a plasticizer, while still separately feeding the polymer powder onto the solid substrates during the coating process [7-9]. Investigations from these researchers encompassed cellulose derivatives, the acrylic polymer Eudragit® RS, and shellac [7-9]. Both methods [6-9] required a minimal amount of water, and it was demonstrated that dry-powder coating compared to aqueous coating procedures generally required higher coating levels, higher plasticizer concentrations, and higher processing temperatures. Nevertheless, the processing time in dry-powder coating operations was significantly shorter due to the high solids content of the coating mixture. Recently the dry coating method developed by Obara was modified by Kablitz et al. by replacing the anti-tacking agent talc with colloidal silicon dioxide and eliminating the use of water in the curing step [10].

A novel water and solvent-free powder coating technique was developed by Cerea et al. and Zheng et al. in 2004 [11, 12]. This dry coating technique did not utilize water or any other liquid during the entire coating process. The process was successfully applied for the acrylic polymers Eudragit® RS PO, Eudragit® RL PO, and Eudragit® E PO for the coating of tablets to modify the drug release rate. Dry powder coating was shown to prevent the aging of the polymeric film, a phenomenon which has been reported for aqueous coated dosage forms during storage. The powder coating process itself consisted of three steps, namely, priming, powder layering, and curing. To facilitate the direct application of the acrylic polymers onto the solid substrates, the solid Eudragit® RS PO and Eudragit® RL PO powders were pre-plasticized using a hot-melt extrusion process. The extrudates were subsequently cryogenically ground into a micronized coating

powder [12]. The pre-plasticization step was not needed for Eudragit® E PO due to the low glass transition temperature of this polymer [11].

Eudragit® L 100-55, an anionic copolymer, is based on methacrylic acid and ethyl acrylate in a 1:1 ratio and has not been studied in dry powder coating applications. Its glass transition temperature was reported to be within the range of 124 to 129ºC [13, 14].

The objective of the present study was to investigate the properties of chlorpheniramine maleate (CPM) and theophylline tablets that were powder-coated with pre-plasticized Eudragit® L 100-55. CPM is a freely water soluble drug. It was reported that CPM pellets required higher coating levels of the enteric polymer than pellets containing theophylline, a less soluble drug, in order to pass the dissolution specification in acidic media due to the migration of the drug into the Eudragit® L 30 D-55 coating [2]. Powder coating, a water and organic solvent-free process, was employed as a method to prevent the migration of the highly water soluble drug CPM into the film coating. The drug release properties of the powder-coated tablets as well as storage stability under accelerated storage conditions were studied. Film formation and surface morphology of powder-coated tablets were characterized, and the function and influence of the primer on powder adhesion and film formation were studied.

4.2 MATERIALS

Eudragit® L 100-55 was donated by Degussa Corp. (Piscataway, NJ). Chlorpheniramine maleate USP/NF, anhydrous theophylline USP, magnesium stearate NF, and lactose monohydrate NF were purchased from Spectrum Chemical Mfg. Corp. (Gardena, CA). Triethyl citrate NF (TEC) was donated by Morflex Inc. (Greensboro, NC). Talc USP (Imperial 500) was supplied by Luzenac America, Inc. (Centennial, CO). Polyethylene Glycol (PEG) 3350 NF was donated by The Dow Chemical Company (Midland, MI). Microcrystalline cellulose (MCC, Avicel® PH-101) was donated by FMC BioPolymer (Newark, DE). Polyvinylpyrrolidone K-30 (PVP, Kollidon® 30) was supplied by BASF Corp. (Mt. Olive, NJ). Colloidal silicon dioxide (CAB-O-SIL® M-5P) was donated by Cabot Corporation (Billerica, MA).

4.3 METHODS

4.3.1 Coating powder preparation and characterization

The pre-plasticization process for Eudragit® L 100-55 was based on the method reported by Zheng et al. [12] for Eudragit® RS and Eudragit® RL PO. After combining Eudragit® L 100-55 with TEC (20, 30, or 40% based on the polymer weight) in a high shear mixer, the powder blend was extruded using a single screw extruder (Randcastle

Model RC 0750, Cedar Grove, NJ). The extruder temperature zones were set to: zone 1 = 80ºC, zone 2 = 110ºC, zone 3 = 115ºC, and die = 120ºC. A cylindrical die with an inner diameter of 6mm was used. The extrudate was subsequently cut into pellets with a Randcastle RCP-2.0 pelletizer and then cryogenically ground into a fine powder using a CF Mikro-Bantam Cryogenic Grinder (Micron Powder Systems, Summit, NJ). To obtain a more uniform particle size distribution and exclude fines and large particles, the ground pre-plasticized polymer was sieved by mechanical shaking for 15 minutes. The particle size fraction between 100 and 200 mesh (75 - 150μm) was used for the dry powder coating experiments.

Laser light diffraction was employed to analyze the particle size distribution of the coating powder using a Malvern Mastersizer S (Malvern Instrument Limited, Malvern, Worcestershire, UK). D_v 10, D_v 50, and D_v 90, the cumulative percent undersize, were determined using the diffractive index of Eudragit® L 100-55 (n_D^{20} = 1.3899). The measurements were performed in triplicate in purified water (n_D^{20} = 1.3300).

The TEC content in the extrudates was determined at a wavelength of 210 nm using a Waters high performance liquid chromatography (HPLC) system (Waters, Milford, MA) equipped with a photodiode array detector (Model 996). Depending on the TEC concentration, 500 mg (20 and 30% TEC) or 300 mg (40% TEC) of processed polymer were initially dissolved in 50 mM pH 7.4 buffer and then 1:2 diluted with 50 mM pH 2.5 phosphate buffer to remove the polymer from the solution (n = 3). The samples were filtered using 0.2 μm nylon filters prior to analysis. 50 μL samples were injected by an autosampler (Model 717plus), and Empower® Version 5.0 software was

used to collect and analyze the data. An ODS-3 3 μm, 150 mm × 4.6 mm column (Alltech Inertsil™, Deerfield, IL, USA) was employed at a column temperature of 30 ± 2ºC. The mobile phase contained a mixture of acetonitrile:pH 2.5 10 mM phosphate buffer in volume ratios of 55:45. The flow rate of 1 mL/min resulted in a retention time of 4.0 min for TEC. Linearity was demonstrated in the concentration range of 100 to 500 μg/mL (R^2 > 0.999).

A MF-50 Moisture Analyzer (A&D Engineering, Inc., Milpitas, CA) was used to determine the loss on drying of the coating powder. A sample of 2 g was dried to a constant weight, as defined by a weight change of less than 0.05% per minute at 110ºC.

4.3.2 Differential scanning calorimetry

To characterize the thermal properties of the melt extrudates, modulated differential scanning calorimetry (MDSC) was conducted using a Thermal Advantage Model 2920 (TA Instruments, New Castle, DE) equipped with Universal Analysis 2000 software. Ultrahigh pure nitrogen was used as the purge gas at a flow rate of 150 ml/min. The polymeric film or polymer powder samples were sealed in aluminum pans (Kit 0219-0041, Perkin-Elmer Instruments, Norwalk, CT). The temperature ramp rate was 3°C/min at a modulation rate of ±1.00°C every 60 seconds. The initial temperature was at least 30ºC below the expected glass transition temperature. The final temperature exceeded the glass transition temperature by a minimum of 10ºC. The reverse heat flow of the second heating cycle was used to determine the inflection glass transition temperature.

To study any potential interactions between PEG 3350 and the model active pharmaceutical ingredients (API), conventional differential scanning calorimetry (DSC) was used employing the same instrument as described above. The samples were heated from 50ºC to 300ºC using a temperature ramp rate of 10ºC/min. The raw materials were analyzed as well as physical mixtures of API and PEG 3350 in ratios of either 1:1, 1:2 or 1:10. The heat flow of the first heating cycle was used to determine the melting points and heat of fusion values.

4.3.3 Tablet preparation

The compositions of CPM and theophylline tablets appear in Table 4.1. The API, Avicel® PH 101, lactose monohydrate, and the binder were mixed in a V-shape blender (Model Yoke, Patterson-Kelley Co., East Stroudsburg, PA) for 15 minutes. Following the addition of the magnesium stearate and colloidal silicon dioxide, the mixture was blended for an additional 5 minutes. The tablets were compressed on a rotary press (Model FJS-B2 Stokes, Bristol, PA) using deep concave 5 mm punches and characterized by their dimensions and weight (Table 4.1). The tablet hardness was measured on a hardness tester (WTP-3, Heberlein &. Co. AG, Wattwil, Switzerland). The disintegration time was determined according to USP 29 using a USP Disintegration Tester (Vankel Industries Inc., Chatham, NJ). The tablet friability was tested according to USP 29 with a Tablet Friability Apparatus (Vankel Industries Inc., Chatham, NJ).

4.3.4 Powder coating process

Powder coating of the tablets was performed according to the method reported by Cerea et al. (2004) and Zheng et al. (2004) in a modified laboratory scale spheronizer (Model 120, G.B. Caleva, Dorset, UK) [11, 12]. The batch size was 40 g of tablets. The rotation speed of the spheronizer was set to 220 rpm. The bed temperature was dependent on the plasticizer content of the coating mixture and maintained at 80-85ºC, 70-75ºC, or 70-75ºC using coating powders containing either 20, 30, or 40% TEC based on the polymer weight, respectively. The temperature of the coating bed was monitored by measuring the surface temperature of the tablets using a Fluke 61 Infrared Thermometer (Fluke Corporation, Everett, WA). Both talc and PEG 3350 were added in a 10% ratio to the coating powder based on the weight of the ground extrudate. The feeding rate of the coating powder onto the tablets cores was dependent on the capacity of the coating powder to adhere, which decreased with increasing coating levels. Following the application of the primer subcoat, the polymer mixture containing pre-plasticized Eudragit® L 100-55 was fed onto the tablet surfaces at a feeding rate of about 3 g/min until a polymer weight gain of 7% was obtained. The powder-feeding rate was then reduced to 0.5 g/min. Due to the poor flow properties of the coating formulation, the powder mixture was manually fed onto the tablet cores. After completion of the coating process, the tablets were subsequently cured either in the operating spheronizer for 6 hours or in a static oven on Teflon trays at 60ºC for 24 hours. To prevent sticking during the stability test at 25ºC/60% RH and 40ºC/75% RH, the cured tablets were over-coated with 2% talc based on the weight of the coated tablets in the spheronizer.

4.3.5 Contact angle measurements

Polymer sample compacts were prepared at a 500 kg compression force using a Carver Laboratory Press (Model M, ISI Inc., Round Rock, TX). 3 μL of water were placed onto the surface of polymer compacts using a microsyringe. The contact angle was determined by measuring the tangent to the curve of the droplet on the surface of the compact using a Goniometer (Model No. 100-00-115, Ramé-Hart Inc., Mountain Lakes, NJ). The measurements were performed in triplicate at 20ºC.

4.3.6 Drug release study

The drug release rate of CPM and theophylline from powder-coated tablets was investigated using a modified USP 29 Drug Release Standard for Enteric-Coated Articles, Method B. *In vitro* dissolution testing was performed in 900 mL 0.1N HCl for the first two hours, followed by 4 hours in 900 mL pH 6.8, 50 mM phosphate buffer solution maintained at 37 °C and agitated at 50 rpm using a USP 29 Apparatus 2 (Vankel VK 7000; Vankel Industries Inc., Cary, NC). The dissolution properties of the coated tablets were determined by placing three tablets into each of either three or six dissolution vessels respectively (n = 3 x 3 tablets/vessel or n = 6 x 3 tablets/vessel). Samples were withdrawn by an autosampler over a 6 hour period (Vankel VK 8000; Vankel Industries Inc., Cary, NC). Samples were analyzed for CPM content using a HPLC system with a photodiode array detector (Model 996, Waters, Milford, MA) at a wavelength of 260 nm. Prior to analysis, the samples were filtered using 0.45 μm nylon filters. The autosampler

(Model 717plus) was set to inject 50 μL samples. The data were collected and analyzed using Empower® Version 5.0 software. An ODS-3 3 μm, 150 mm × 4.6 mm column (Alltech Inertsil™, Deerfield, IL, USA) was used. The column temperature was kept at 40 ± 2ºC. The mobile phase contained a mixture of water:methanol:triethylamine in volume ratios of 675:325:4.5. The retention time of the CPM was 9.5 min. Linearity was demonstrated from 2 to 50 μg/mL ($R^2 > 0.999$). The quantitative analysis for theophylline was conducted using the HPLC method described by Zheng et al. 2004 [12]. The same equipment was used as for the quantitative analysis of CPM. The injection volume was 40μL. The mobile phase consisted of water:acetonitrile:glacial acid in volume ratios 845:150:5 and 1.156 g/L of sodium acetate trihydrate. The flow rate was 1 mL/min, and the retention time was 4 minutes. Linearity was confirmed from 1 to 60 μg/mL ($R^2 > 0.999$).

4.3.7 Film preparation

The ground extrudate containing varying amounts of PEG 3350 was pressed into polymeric films in Teflon coated aluminum dishes with a Teflon coated lid by applying a small weight. A compression force of 45 g per cm^2 during the curing process was used to prepare the polymeric film to facilitate polymer particle fusion and film formation. This pressure minimized the formation of voids in the film due to an increase in the packing density of the polymer powder. The films were stored at 60ºC in a static oven for 24 hours.

4.3.8 Scanning electron microscopy

The morphology of the surface and cross-section of powder-cast films and coated tablets was analyzed by scanning electron microscopy (SEM) using a Hitachi, Model S-4500 FE (Hitachi, London UK) operated at 10 kV and 20 mA. The samples were sputter coated with gold/palladium (60:40) using a Ladd Benchtop Sputter Coater (Ladd Research, Winston, VT) at 2.5 kV and 20 mA for 75 seconds.

4.4 RESULTS AND DISCUSSION

4.4.1 Coating powder preparation

Due to the high glass transition temperature of the bulk polymer and to reduce the melt viscosity, the Eudragit® L 100-55 was pre-plasticized with up to 40% TEC using hot-melt extrusion. The pre-mixing of polymer and plasticizer under high shear conditions allowed for a homogeneous distribution of the plasticizer in the extrudate. The temperature in the metering zone of the extruder (zone 3) was maintained at 115ºC. Processing temperatures for Eudragit® L 100-55 should generally not exceed 130ºC as a decrease in functional groups was reported above temperatures of approximately 130ºC, with depolymerization occurring at temperatures exceeding 300ºC [15].

The TEC content recommended for aqueous coating dispersions of Eudragit® L 100-55 is 10-15% based on the dry polymer weight. In previous reports, Obara et al. and

Pearnchob et al. demonstrated that dry powder coating of tablets and pellets required polymers with higher plasticizer levels than normally employed in aqueous coating processes [6-9]. The extrusion of Eudragit® L 100-55 containing 10% TEC (based on the polymer weight) was unsuccessful due to the high melt viscosity of the polymer. A thermal glidant could be used to aid in processing, but may impact dissolution. Thus, the current study investigated plasticizer ratios of 20, 30, and 40% TEC.

The glass transition temperature of the polymer was dependent on the amount of plasticizer in the extrudate, as seen in Table 4.2. A homogeneous distribution of the plasticizer throughout the polymer was verified for all TEC concentrations, as evidenced by the low standard deviation of the TEC recovery values. The higher the plasticizer level, the more difficult was the feeding of the polymer-plasticizer mixture from the hopper into the extruder barrel due to the poor flow properties of the powder-plasticizer mixture. The low glass transition temperatures of the pre-plasticized polymeric extrudates required a cryogenic grinding process to obtain a fine powder suitable for powder coating applications.

The loss on drying of the coating powder was analyzed to determine the moisture content since water is a known plasticizing agent for acrylic polymers [16] and adsorbed moisture has been shown to significantly impact the glass transition temperature for Eudragit® L 100-55 [13]. The loss on drying of the processed polymer ranged from 3.1 to 3.8%, which was slightly lower than the value of 4.5% for the bulk polymer (Table 4.2). Before the analysis, it was demonstrated by thermogravimetric analysis that TEC was not volatile at the 110ºC storage temperature used in this study (data not shown). However, TEC exhibited a distinct weight loss at temperatures above 200ºC.

The particle size distributions of the unprocessed Eudragit® L 100-55 and ground, pre-plasticized polymer after sieving are presented in Table 4.2. The particle sizes of the processed polymers were significantly higher than the commercially available Eudragit® L 100-55 powder but equivalent to particles used in previous powder coating studies [12]. Due to identical processing conditions and the same sieving process, no influence of the plasticizer level on the particle size distribution of the cryogenic ground powders was observed.

4.4.2 Powder coating

The coating powder mixture was composed of the processed polymer, 10% talc, and 10% PEG 3350. Both the weight of talc and the weight of PEG 3350 were based on the weight of the ground extrudate. A talc content of 10% effectively prevented tablet aggregation during the powder coating process with pre-plasticized Eudragit® L 100-55. Comparably low levels of talc as an anti-tack agent were sufficient due to the absence of liquids during the coating operation, and low talc levels had previously been successfully employed in a powder coating process with Eudragit® E PO and Eudragit® RS/RL PO [11, 12].

Powder adhesion to the core tablets of pre-plasticized Eudragit® L 100-55 combined with 10% talc was not possible without the presence of a primer subcoat. Several primers were investigated including cetyl alcohol, poloxamer 407, and PEG 3350. All investigated priming agents had a melting point below the coating temperature in order to generate a liquid priming layer covering the core tablets. The interfacial

interactions between the tablet surface and the pre-plasticized polymer particle are complex and are dependent on interfacial tension, wetting and adhesion [17, 18]. Another factor influencing the adhesion of the coating powder is the hydrophilicity of the tablet surface. PEG 3350, which is characterized by a small contact angle with purified water, increases the hydrophilic surface properties of the tablet [12]. The use of low melting point hydrophobic primers, such as cetyl alcohol, were not effective in powder-coating with pre-plasticized Eudragit® L 100-55, although they were successfully employed for Eudragit® RS/RL PO [12]. Since Eudragit® L 100-55 was characterized by a contact angle with water of 61.0 ± 2.6º (n = 3), while the contact angle of Eudragit® RS PO and RL PO was determined to be 87.7 ± 2.1º and 86.7 ± 0.6º respectively (n=3), Eudragit® L 100-55 is a more hydrophilic polymer which required a more hydrophilic priming agent.

PEG 3350 was not only employed as a priming agent, but it was also incorporated into the coating powder at the 10% level based on the weight of the ground extrudate. When PEG 3350 was utilized as the priming agent but was not present in the powder coating formulation the maximum polymer weight gain that could be achieved was 5%, which was insufficient to pass the gastric phase of the USP enteric test for all TEC levels investigated. To investigate the miscibility of PEG 3350 and Eudragit® L 100-55 and to study the influence of PEG 3350 on the thermal properties of Eudragit® L 100-55, polymeric films were powder-cast and cured for 24 hours at 60ºC. The presence of the PEG 3350 at the 10% level reduced the glass transition temperature of Eudragit® L 100-55 by about 30ºC for all TEC levels as shown in Table 4.2. The thermograms indicated complete miscibility of Eudragit® L 100-55 and PEG 3350 at this ratio, as evidenced by a single detectable glass transition and the absence of the distinct melting peak of PEG

3350. These findings correlate well with previously published solubility parameters, which suggest a high affinity between PEGs and the Eudragit® L polymers [19].

The influence of PEG 3350 on film formation was additionally investigated in a second free film study. The SEM micrographs of cross-sections of Eudragit® L 100-55 films containing 30% TEC and various levels of PEG 3350 are presented in Figure 4.1. PEG 3350 levels of 5 and 10% promoted polymer particle fusion and facilitated film formation during the curing process at 60ºC for 24 hours. However, the addition of 5% PEG 3350 to the coating powder in combination with a primer did not promote polymer adhesion. In contrast, a 3% weight gain of PEG 3350 as primer and the additional incorporation of 10% PEG 3350 into the coating powder allowed high coating levels with polymer weight gains above 15% for all employed TEC levels.

The bed temperatures for the powder coating process were 80-85ºC, 70-75ºC, or 70-75ºC for powder blends containing 20, 30, and 40% TEC, respectively. These temperatures are above the glass transition temperature of the pre-plasticized Eudragit® L 100-55 for the respective TEC concentrations.

The influence of TEC content and coating level on the release rate of CPM from powder-coated tablets is presented in Figure 4.2. Tablet samples were withdrawn during the coating process after each designated coating level was reached and cured for 24 hours in a static oven. The applied polymer weight gain had a significant impact on the drug release properties of the powder-coated tablets. The USP 29 Drug Release Standard for Enteric-Coated Articles requires a drug release of less than 10% after 2 hours dissolution testing in 0.1N HCl. In addition, the gastric stability was found to be significantly dependent on the TEC concentration in the film coating. A coating level of

10% polymer weight gain on powder-coated CPM tablets met the USP dissolution specifications at a TEC content of both 30 and 40%. However, a polymer weight gain of 15% was needed to maintain the release of CPM in acid below the 10% level for a TEC content of 20%. Higher plasticizer levels will enhance the coalescence between the polymer particles and were previously demonstrated to decrease drug release rates [20]. This trend was observed both in the gastric as well as the buffer phase of the enteric test.

To investigate the surface morphology of the coating, powder-coated tablets with a 15% polymer weight gain were subjected to microscopic examination as seen in Figure 4.3. The highest coating level was chosen to evaluate the dependence of film formation on the plasticizer level in the coating powder. All TEC concentrations resulted in the formation of a dense polymer film as seen in the micrographs of the cross sections. The surfaces of all films, however, were characterized by the presence of voids and non-fused large particles of polymer. The number of flaws in the film coating decreased with increasing TEC levels, thereby demonstrating improved film formation at elevated plasticizer concentrations in the polymeric film. The results of the microscopic analysis supported the observed differences in CPM dissolution rates at different plasticizer levels.

Swelling of the enteric coating was observed for the powder-coated CPM tablets during dissolution testing after immersion in 0.1N HCl for 2 hours. Following the acid stage of the enteric test, the tablets were characterized by an increase in size and a soft consistency compared to the dry tablets. These results may be partially attributed to the high level of water-soluble components in the film coating. TEC has been shown to be slowly released from Eudragit® L film coatings due to strong interactions with Eudragit® L compared to other plasticizers [21]. PEGs have been studied by other researchers to

increase the permeability of poly(meth)acrylate films. Due to its high water solubility, PEG can act as a pore forming agent during dissolution testing depending on the miscibility with the polymer and can cause an increase in the drug diffusion rate [22-24]. Since water molecules are strongly bound to the ether groups in the PEG molecule by hydrogen bonds [19], the PEG remaining in the polymeric film causes swelling of the polymer coating, resulting in the release of a small amount of CPM during the acid stage of the enteric test. This level of drug release did not exceed the maximum allowance of the USP test for enteric-coated articles at coating levels of 10% polymer weight gain and above.

High levels of plasticizer also increase the tackiness of a polymeric film. This effect improves adhesion of the polymer film to the tablet core, but represents an undesired phenomenon in coating operations and during storage, and may result in agglomeration of coated dosage-forms [25, 26]. Increasing tackiness with high TEC levels (40%) was also observed for the powder coating of tablets with pre-plasticized Eudragit® L 100-55 following curing. Tackiness was eliminated with the application of a 2% talc overcoat in the spheronizer after the curing step.

A TEC content of 30% in the processed polymer and a coating level of 10% polymer weight gain were determined to be the ideal coating parameters for CPM tablets since tablets coated with Eudragit® L 100-55 containing 20% TEC required high coating levels, while a TEC content of 40% resulted in slightly tacky tablets. Tablets powder-coated using these conditions were further studied to investigate the optimal curing conditions and the physical stability of the powder-coated tablets at accelerated storage conditions. This formulation was also used to coat tablets containing theophylline, a less

soluble drug.

4.4.3 Curing conditions

In Figure 4.4, the scanning electron micrographs are presented which show the surface and cross-section of an uncured tablet that was powder-coated with pre-plasticized Eudragit® L 100-55. Film formation was incomplete following the application of the coating material using the dry powder coating process. The upper layer of the polymer film is characterized by separate polymer particles, while the lower layer exhibited a dense polymeric film. Without curing, the quantity of drug released in the acidic medium was higher than 10%, which is the maximum allowance by the USP 29 Release Standard for Enteric-Coated Articles, and exhibited a large standard deviation. Since a curing time of 24 hours in a static oven resulted in a continuous polymeric film in previous powder-coating studies [11, 12], all tablets used in the dissolution studies presented in Figure 4.2 were cured for 24 hours at 60ºC. Curing at 80ºC resulted in yellow discoloration of the tablets, due to the oxidation of PEG at this high temperature [27, 28]. A curing condition at 60ºC for 24 hours prevented the discoloration. A curing study was performed to determine the necessary curing time at 60ºC to reduce the drug release in 0.1N HCl to less than 10%.

The tablets were coated with pre-plasticized Eudragit® L 100-55 containing 30% TEC based on the polymer weight with a 10% polymer weight gain. After the completion of the coating process, the tablets were either cured in a static oven at 60ºC or were tumbled in the spheronizer at 60ºC at 220 rpm. The gastric stability of the powder-coated

tablets was investigated, which was characterized by the percent of CPM released in 0.1N HCl after 2 hours using USP 29 Apparatus 2. The data in Figure 4.5 show the influence of curing time and conditions on the CPM release rate from tablets powder-coated with pre-plasticized Eudragit® L 100-55.

Curing of powder-coated CPM tablets at 60ºC improved gastric stability and decreased the variability in the dissolution data since curing eliminated the residual voids between the polymer particles. In prior studies, curing was shown to be an essential step in a dry-powder coating process to improve polymer particle fusion and complete film formation [6-9, 11, 12]. Curing in the spheronizer was demonstrated to be an efficient curing method with a small standard deviation and a lower average CPM release rate in the acidic medium than the oven cured tablets. Due to the strong centrifugal forces and the resulting impact of the tablets on the spheronizer wall, the polymer particles were compressed, deformed, and fused. The surface was leveled and defects were corrected faster resulting in a shiny surface compared to the oven cured tablets, even after short curing times. Curing in the spheronizer also reduced the influence of gravity on the polymer flow during film formation. Generally, the flow of polymeric films with a thickness of 25 - 75 μm or above is controlled by gravity [29]. In the case of powder-coated tablets, this effect caused the direction of flow of the polymer to the bottom of the tablet. As a result, tablets stored on trays at 60ºC for 24 hours developed a flat base which resulted in the loss of the round tablet shape. After rotating for 12 hours, tablets cured in the spheronizer showed signs of deformation and grey discoloration of the tablet edges. Curing in the spheronizer should therefore generally not exceed 6 hours to prevent this phenomenon.

Curing in both a static oven and the spheronizer was shown to be effective for tablets powder-coated with pre-plasticized Eudragit® L 100-55, to achieve sufficient gastric stability. However, curing in the spheronizer reached equilibrium faster than curing the powder-coated tablets in a static oven.

4.4.4 Properties of powder-coated theophylline tablets

Dosage forms containing theophylline were shown to require a lower Eudragit® L 30 D-55 coating weight gain applied from an aqueous dispersion compared to those containing CPM to provide sufficient gastric stability [2]. This phenomenon was attributed to the lower water solubility of theophylline and decreased migration rate of the API into the film. Thus, theophylline was selected for this study to compare and characterize its release rate from tablets powder coated with pre-plasticized Eudragit® L 100-55 using the same parameters as for CPM.

Theophylline containing tablets (Table 4.1) were powder-coated with a pre-plasticized blend of Eudragit® L 100-55 containing 30% TEC. The tablets were coated to polymer weight gains of 7, 10, and 15% and then subsequently cured in a static oven for 24 hours. The static oven and not the spheronizer was used for curing to compare the results to the CPM tablets. The influence of weight gain on the release rate of theophylline from tablets powder-coated with pre-plasticized Eudragit® L 100-55 containing 30% TEC based on the polymer weight is seen in Figure 4.6. A polymer weight gain of 7% provided gastric stability with the amount of drug released after two hours in 0.1N HCl being approximately 10%. A 10 and 15% polymer weight gain

reduced the amount of drug released after two hours in 0.1N HCl to less than 5 and 2% respectively. The drug release from theophylline tablets could be controlled with a lower polymer weight gain. The differences in the drug release rates are mainly caused by the higher water solubility of CPM and higher drug diffusion from CPM tablets compared to the theophylline tablets in acidic media. It has been reported that the drug release rate from theophylline tablets was slower compared to tablets containing a more water soluble API [30]. Drug release during the acid phase is a result of swelling of the film coating, water penetration into the core, drug dissolution, and subsequent diffusion through the hydrated polymeric film [31]. Penetrated water increases the polarity and molecular mobility inside the tablet [30]. Both water influx and drug solubility are factors which increase the drug release rate through enteric polymer films [31]. The transfer of drug through polymeric films is not only controlled by diffusion, but is also modulated by osmotic pressure [32]. Osmotic forces that are generated by the dissolution of drug and excipients in the tablet matrix increase the influx of water and the diffusion of electrolyte, which result in faster drug release [33].

The theophylline core tablets were characterized by a significantly shorter disintegration time compared to the CPM tablets. The tablet size, weight, hardness, and friability were similar for both formulations. To investigate possible API migration into the polymer film during the powder coating process or curing, the interactions between the model drugs and the molten PEG 3350 were studied using conventional DSC. The first heating cycle was used to investigate the effects of the molten PEG 3350 on each crystalline drug. The DSC profiles of the raw materials were characterized by distinct melting peaks as seen in Figure 4.7. PEG 3350 melted at a temperature of 61ºC. The

melting points of CPM and theophylline occurred at 136ºC and 274ºC, respectively, which were above the coating and curing temperature conditions. The melting point as well as the heat of fusion of PEG 3350 was not influenced by the presence of either CPM or theophylline. In contrast, the DSC profiles of the physical mixtures, exhibit lower or no distinct melting points for both APIs, depending on the mixing ratio. Additionally, PEG 3350 influenced the heat of fusion of both APIs. Table 4.3 shows the heat of fusion values of the individual components calculated based on the mixing ratio of the model drug and PEG 3350. All physical mixtures exhibited a lower heat of fusion for both CPM and theophylline in a physical mixture compared to the pure drugs, indicating changes in the crystal lattice of the model compounds. Both theophylline and CPM were shown to interact with PEG 3350. The melting point of CPM is lower than that of theophylline and hence closer to the processing conditions. Consequently the effect of PEG 3350 could be more pronounced on CPM than on theophylline.

The theophylline release rate in buffer was faster compared to the CPM release rate. The dissolution of enteric polymeric films during the buffer phase of the enteric test was demonstrated to occur primarily at the polymer/bulk interface rather than by bulk erosion throughout the coating layer [31]. As a result, the thickness of the polymeric film was shown to decrease under simulated intestinal conditions. The drug CPM was previously shown to adsorb to Eudragit® L 30 D-55 as a function of the pH of the dissolution medium [2]. Consequently the theophylline release rate in pH 6.8 buffer was expected to be faster and less dependent on the coating level.

4.4.5 Stability of powder-coated CPM tablets

Powder-coated tablets have been reported to demonstrate excellent physical stability during storage [6-8, 12]. The physical stability of CPM tablets powder-coated with a 10% weight gain of pre-plasticized Eudragit® L 100-55 containing 30% TEC based on the polymer weight was determined. These tablets were cured in the rotating spheronizer at 170 rpm for 6 hours. After the completion of the curing step, a 2% talc overcoat was applied onto the coated tablets in the spheronizer to reduce the tackiness of the film coating. The powder-coated tablets were stored in induction-sealed HDPE containers with desiccant to exclude the influence of humidity during storage at both 25ºC/60% RH and 40ºC/75% RH. Before dissolution testing, the samples were equilibrated to ambient temperatures for 24 hours.

As shown in Figure 4.8, CPM powder-coated tablets demonstrated excellent stability over 12 weeks at 25ºC/60% RH with no detectable difference in the drug release profiles. The drug release rate from powder-coated tablets stored at 40ºC/75% RH was characterized by an initial increase over 4 weeks followed by a slight decrease after 8 and 12 weeks. The drug release profiles that were obtained from tablets stored at 40ºC/75% RH after one and eight weeks were excluded from Figure 4.8 for better clarification between the single profile curves. Both deleted graphs were similar to the initial drug release curve. This aging phenomenon was attributed to the additional plasticization of the Eudragit® L 100-55 by PEG 3350 during storage. The glass transition temperature of the coating powder containing 30% TEC based on the polymer weight and 10% PEG based on the ground extrudate was approximately 28ºC as shown in Table 4.2.

This temperature was below the storage temperature. The changes in dissolution rate during storage can be explained by changes in the permeability of the coating that resulted from increased molecular mobility.

4.5 CONCLUSION

Dry powder coating, a completely liquid free process, was demonstrated to be an efficient method to enterically coat tablets with Eudragit® L 100-55. Unlike aqueous coating, powder coating minimized partitioning of the drug into the film coating during the coating process. The choice of primer significantly impacted the film formation and drug release properties. PEG 3350 was determined to be an ideal priming material for powder coating of tablets with pre-plasticized Eudragit® L 100-55. Curing is a necessary step to ensure the complete film formation and drug release stability. The drug release properties of powder-coated tablets were dependent on the curing time, coating level and plasticizer content. Higher TEC levels in the acrylic polymer reduced the polymer weight gain required to control the drug release in 0.1N HCl. The drug release rate from powder-coated theophylline tablets was controlled with slightly lower coating levels. The stability of the powder-coated CPM tablets was confirmed at 25ºC/60% RH over a storage time of 12 weeks.

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4.7 TABLES AND FIGURES

Table 4.1: Chlorpheniramine maleate and theophylline tablet formulations and tablet characteristics (standard deviation, $n = 6$).

	CPM tablets	Theophylline tablets
	Tablet formulations	
API	15%	
Avicel® PH 101	46.25%	
Lactose monohydrate	35%	
Kollidon® 30	3%	
Cab-O-Sil® M-5P	0.25%	
Magnesium stearate	0.5%	
	Tablet characteristics ($n = 6$)	
Diameter (d) [mm]	5.0 ± 0.0	5.0 ± 0.0
Height (h) [mm]	4.2 ± 0.0	4.2 ± 0.0
Weight [mg]	81.2 ± 0.5	82.6 ± 0.3
Hardness [kg]	7.8 ± 0.6	7.8 ± 0.4
Disintegration time [min]	21	1
Tablet friability [%]	0.04	0.01

Table 4.2: Coating powder characteristics: TEC recovery, inflection glass transition temperature (T_g) (standard deviation, $n = 3$), and particle size distribution.

TEC content	**0 (bulk)**	**20**	**30**	**40**
TEC recovery	-	98.5 ± 0.3%	97.5 ± 0.2%	97.5 ± 0.3%
T_g	123.7 ± 0.6ºC	73.7 ± 0.6ºC	61.3 ± 3.1ºC	37.0 ± 2.2ºC
Loss on drying	4.50 ± 0.05%	3.07 ± 0.08%	3.77 ± 0.18%	3.25 ± 0.09%
T_g after addition of 10% PEG 3350	122.2 ± 3.0ºC	47.4 ± 9.0ºC	29.2 ± 0.9ºC	11.1 ± 2.9ºC
Particle size distribution				
D_v 10	0.37 μm	0.33 μm	35.13 μm	38.42 μm
D_v 50	43.63 μm	74.18 μm	77.50 μm	81.94 μm
D_v 90	83.25 μm	148.33 μm	147.58 μm	151.07 μm
Span	1.900	1.995	1.451	1.375

Span index: (D_v90 – D_v10) / D_v50.

Table 4.3: Heat of fusion of CPM, theophylline, and PEG 3350 and their mixtures.

		CPM/PEG mixtures		**Theophylline/PEG mixtures**	
		CPM	PEG 3350	Theophylline	PEG 3350
Heat of fusion [J/g]	Bulk	121.2	194.6	167.1	194.6
	1:1	86.5	194.2	79.0	206.6
	1:2	73.7	196.4	69.8	202.5
	1:10	33.1	193.7	19.3	200.9

Figure 4.1: Influence of PEG 3350 content on morphology of free films prepared from HME processed Eudragit® L 100-55 pre-plasticized with 30% TEC (based on the polymer weight) after curing at 60ºC for 24 hours. A: 0% PEG 3350. B: 1% PEG 3350. C: 5% PEG 3350. D: 10% PEG 3350.

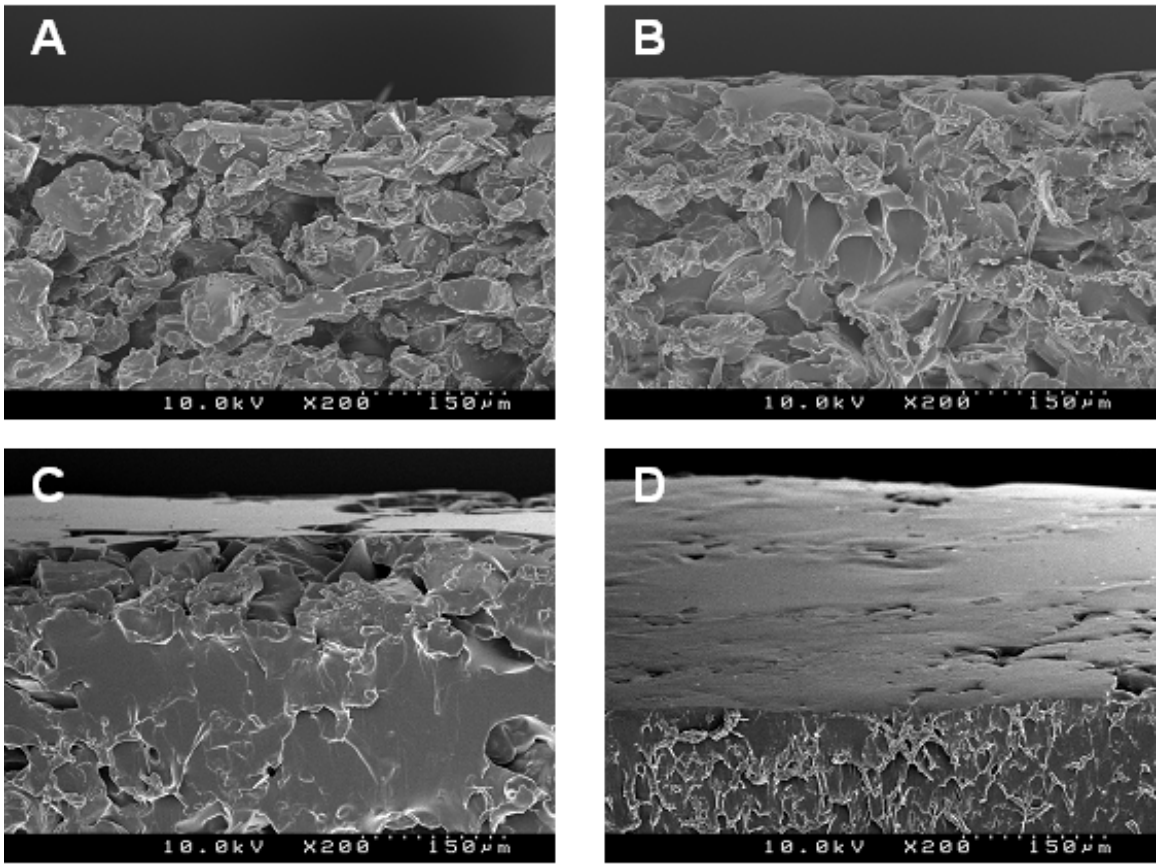
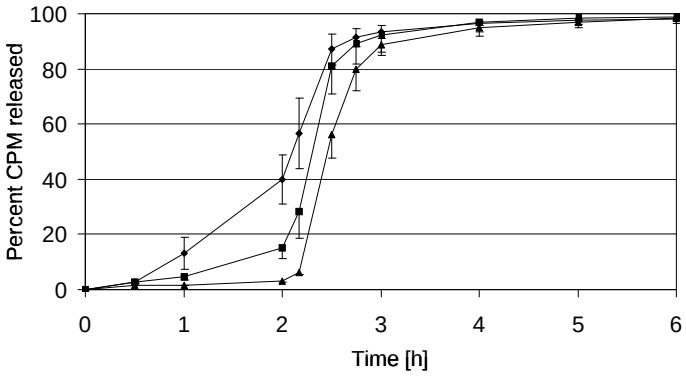


Figure 4.2: Influence of TEC content and coating level on the release of CPM from tablets powder-coated with pre-plasticized Eudragit® L 100-55 using USP 29 apparatus 2. Dissolution in 900mL of 0.1N HCl for 2 hours followed by 4 hours in 900mL pH 6.8 50mM phosphate buffer at 37ºC and 50 rpm. ♦: 7% polymer weight gain. ■: 10% polymer weight gain. ▲: 15% polymer weight gain. (Standard deviation, n = 6 x 3 tablets/vessel.) (A) 20% TEC based on the polymer weight. (B) 30% TEC based on the polymer weight. (C) 40% TEC based on the polymer weight.



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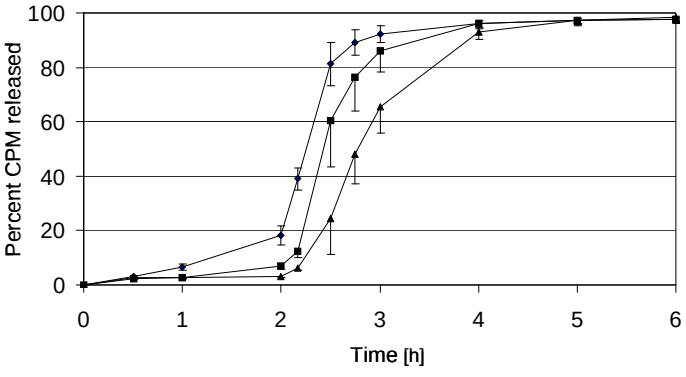

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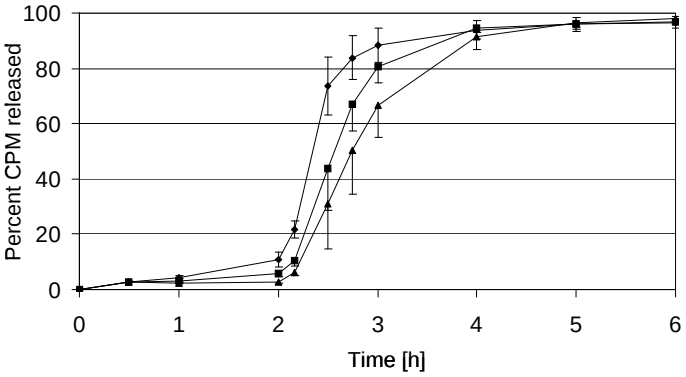


(C)

Figure 4.3: SEM micrographs of cross-section (CS) and surface (SF) of powder-coated tablets (15% polymer weight gain) after curing in a static oven at 60ºC for 24 hours. A: 20% TEC based on the polymer weight (CS). B: 30% TEC based on the polymer weight (CS). C: 40% TEC based on the polymer weight (CS). D: 20% TEC based on the polymer weight (SF). E: 30% TEC based on the polymer weight (SF). F: 40% TEC based on the polymer weight (SF).

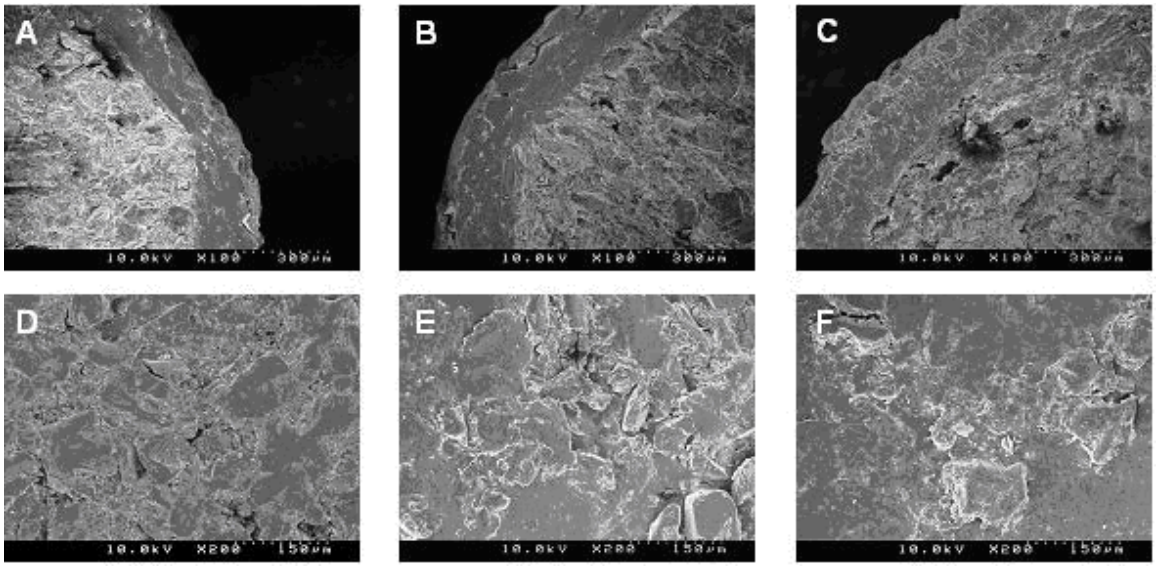


Figure 4.4: SEM micrographs of cross-section (A) and surface (B) of tablets powder-coated with Eudragit® L 100-55 containing 30% TEC based on the polymer weight before curing.

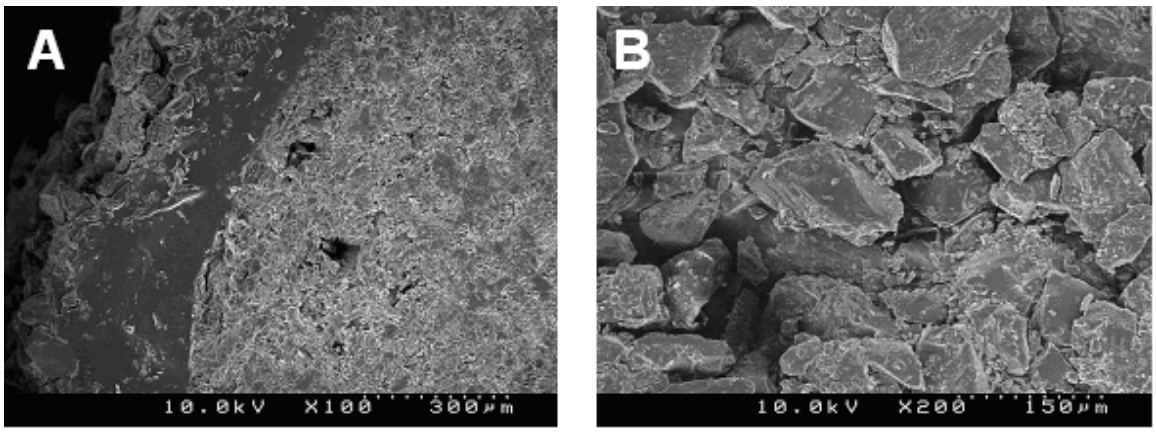


Figure 4.5: Influence of curing time and conditions on the release of CPM from powder-coated tablets (30% TEC based on the polymer weight, 10% polymer weight gain) in 900mL 0.1N HCl using USP Apparatus 2 at 50 rpm and 37ºC after 2 hours. ▲: 60ºC, static oven. ■: 60ºC, revolving spheronizer at 220 rpm. (Standard deviation, n = 3 x 3 tablets/vessel.)

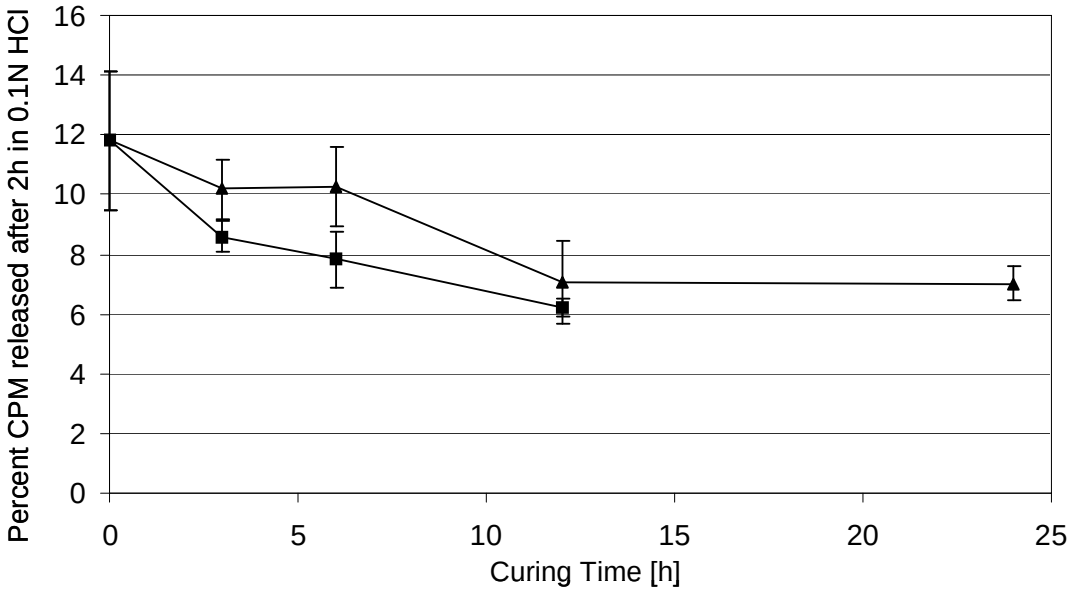


Figure 4.6: Influence of coating level on the release of theophylline from tablets powder-coated with pre-plasticized Eudragit® L 100-55 containing 30% TEC based on the polymer weight using USP 29 apparatus 2. Dissolution in 900mL of 0.1N HCl for 2 hours followed by 4 hours in 900mL pH 6.8 50mM phosphate buffer at 37ºC and 50 rpm. ♦: 7% polymer weight gain. ■: 10% polymer weight gain. ▲: 15% polymer weight gain. (Standard deviation, n = 6 x 3 tablets/vessel.)

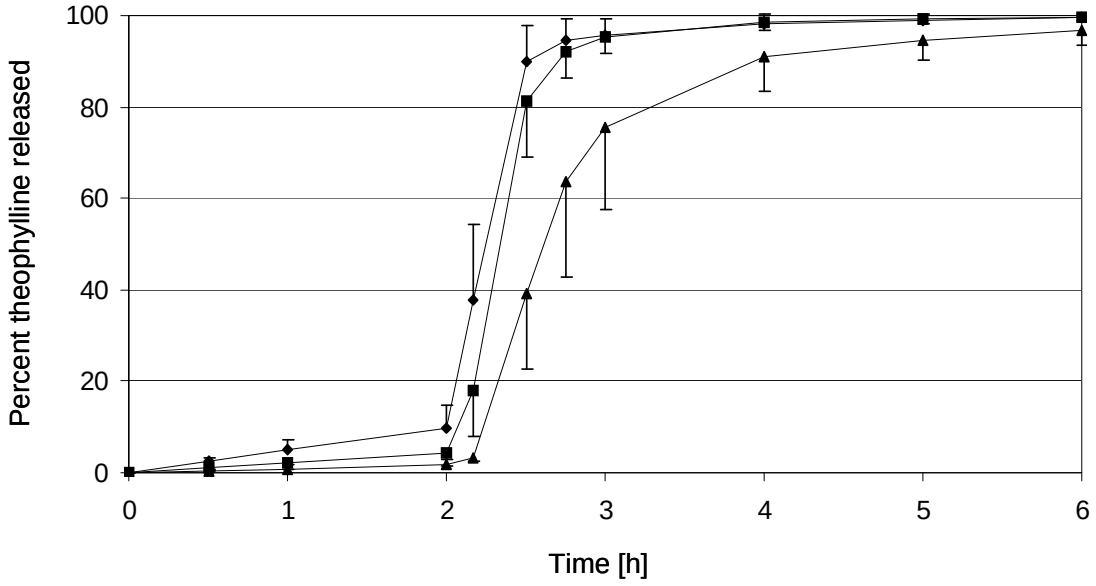
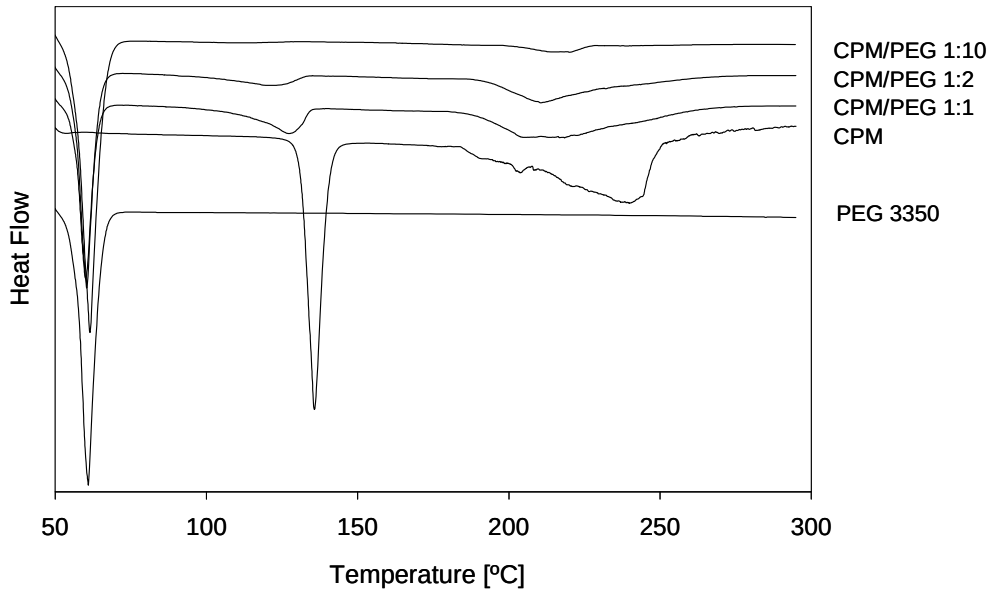
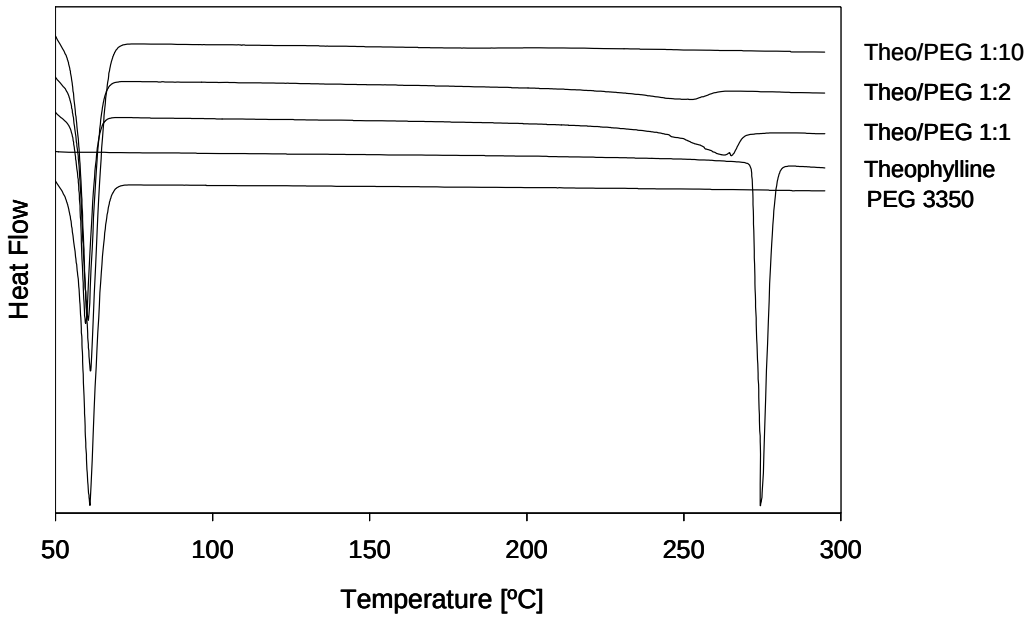


Figure 4.7: DSC profiles of CPM (A) and theophylline (B) and their physical mixtures in ratios of 1:1, 1:2, and 1:10 PEG 3350.

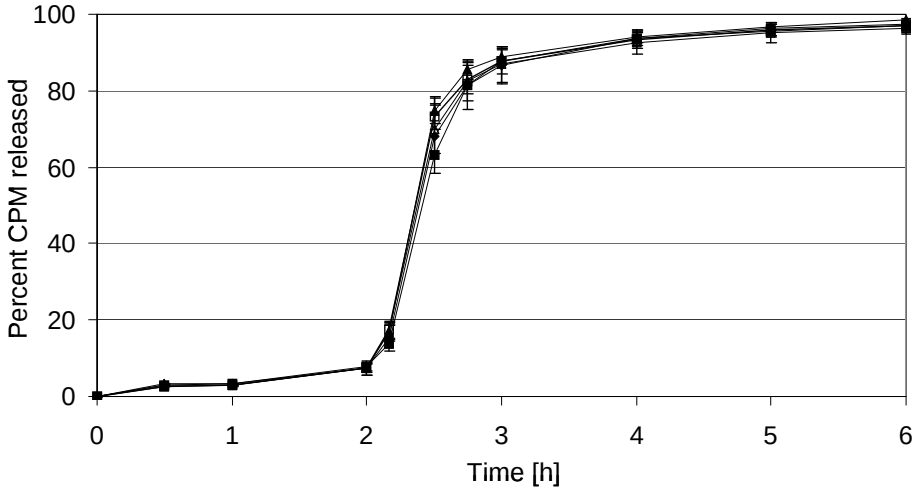


(A)

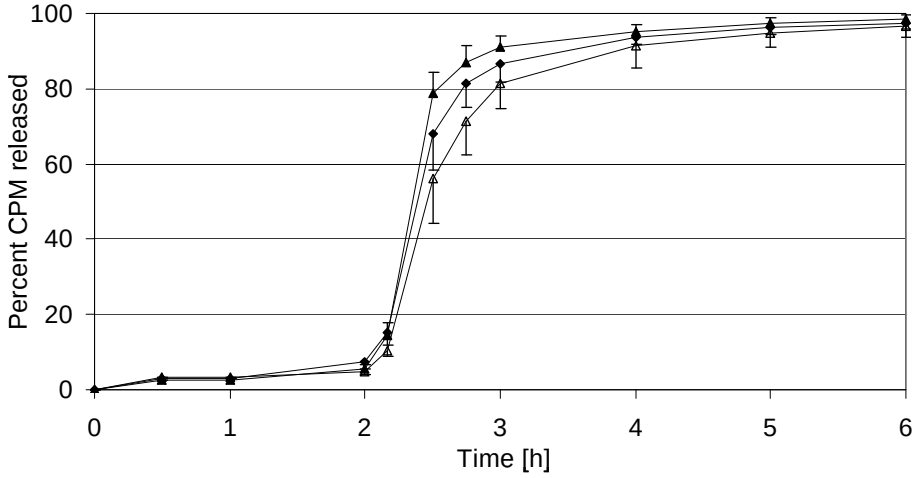


(B)

Figure 4.8: 12 week stability of CPM tablets powder-coated with pre-plasticized Eudragit® L 100-55 containing 30% TEC based on the polymer weight using USP 29 apparatus 2. Dissolution in 900mL of 0.1N HCl for 2 hours followed by 4 hours in 900mL pH 6.8 50mM phosphate buffer at 37ºC and 50 rpm. Polymer weight gain: 10%. ♦: initial. ■: 1 week. ▲: 4 weeks. □: 8 weeks. Δ: 12 weeks (Standard deviation, n = 6 x 6 tablets/vessel). (A) 25ºC / 60% RH. (B) 40ºC / 75% RH.



(A)



(B)

Chapter 5: Investigate the Influence of Polymeric Subcoats on the Drug Release Properties of Tablets Powder-coated with Pre-plasticized Eudragit® L 100-55

Abstract:

The aim of the study was to investigate the properties of sodium valproate tablets that were dry powder coated with pre-plasticized Eudragit® L 100-55. Polyethylene glycol 3350 (PEG 3350) was used as primer to facilitate initial coating powder adhesion. Solubility parameters were employed to determine the wetting properties of the PEG 3350 primer. Additional PEG 3350 within the powder coating formulation was required to enable powder adhesion to the tablet cores. The application of a subcoat of either Eudragit® E PO or Eudragit® RL PO facilitated adhesion of the enteric polymer to the tablet cores and reduced the amount PEG 3350 required in the coating formulation. Since reduction of the PEG 3350 content produced less hydrophilic films, the enteric coating level necessary to control the drug release was decreased. The storage stability of the coated tablets was also improved by the use of an acrylic subcoating material. PEG 3350 and Methocel® K4M were incorporated in both Eudragit® E PO and Eudragit® RL PO subcoating formulations as pore forming agents. The influence of the pore forming excipients on physicochemical properties of free powder-cast films was investigated. The miscibility of the PEG 3350 and Methocel® K4M in the film coating was correlated with their ability to function as pore forming agent.

5.1 INTRODUCTION

Dry powder coating of pharmaceutical dosage forms was first investigated by Obara and coworkers in the late 1990s [1]. The process was later modified by Pearnchob et al. and Kablitz et al. [2, 3]. Recently a new liquid free coating technique for tablets was developed by Cerea et al. and Zheng et al. using the acrylic polymers Eudragit® E PO and mixtures of Eudragit® RL PO and RS PO [4, 5]. The process did not require the use of organic solvents or water. Powder coating is a suitable technique for water-sensitive drugs and can reduce interactions between the API and functional polymers in aqueous coating applications. Powder coating has been shown to significantly reduce processing times [2], prevent aging of polymer films [5], and reduce the migration of drugs into functional coatings [6].

Sodium valproate is a very water-soluble, heat-stable, deliquescent salt with a pKa of 4.8 [7]. It has been reported that sodium valproate tablets and pellets required high coating levels of an enteric polymer, even with the application of either a Methocel® E5 or Opadry® AMB subcoat [8]. Several mechanisms have been proposed in the literature to explain why cores containing highly soluble model drugs require high coating levels of a functional polymer to control the drug release. In aqueous coating operations, highly water-soluble active pharmaceutical ingredients (APIs) can dissolve and partition into the film coating, which may compromise film integrity during dissolution [9]. In this case, an elevated polymer weight gain is required to control the drug release. Other researchers have found that high levels of an enteric polymer are

necessary to delay drug release of an alkaline API in acidic media [10, 11]. The presence of a weak base in the core formulation of an enteric coated dosage form was shown to cause high absorption of simulated gastric fluid and premature drug release at low coating levels [10]. Dissolution of sodium valproate, as a weak base, may increase the microenvironmental pH at the film interface causing partial polymer ionization and premature drug release. A decrease in the drug release in acidic media was observed following the addition of small amounts of organic acids to the sodium valproate core formulation [8].

Subcoating materials have been widely used in combination with enteric polymers to promote adhesion of the functional polymer [1], function as a moisture barrier [12], and prevent interactions between an API and enteric coating [13]. Other researchers described an increased gastric resistance of enteric coated dosage forms in the presence of a polymeric subcoat [14-16].

Eudragit® L 100-55 is an anionic copolymer based on methacrylic acid and ethyl acrylate. The ratio of free carboxyl groups to the ester groups is approximately 1:1. The carboxylic groups ionize in aqueous media at pH 5.5 and above. Eudragit® E PO is a copolymer of dimethylaminoethyl methacrylate and neutral methacrylic esters, and, due to its solubility below pH 5.5, is mainly used for taste-masking or moisture protection. Eudragit® RL PO is a water-insoluble polymer based on ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride in a ratio of 1:2:0.2 and used for sustained release applications. Eudragit® L 100-55, Eudragit® E PO, and Eudragit® RL PO have been used in previous studies of dry powder coating applications [4-6].

The objective was to study the influence of the sub-coating materials Eudragit® E PO and Eudragit® RL PO on the level of enteric coating required for enteric protection. The effect of pore forming agents on the permeability and thermal properties of the polymeric subcoats was also studied.

5.2 MATERIALS

Eudragit® L 100-55, Eudragit® RL PO, and Eudragit® E PO were donated by Degussa Corp. (Piscataway, NJ). Sodium valproate USP/NF and magnesium stearate NF were obtained from Spectrum Chemical Mfg. Corp. (Gardena, CA). Triethyl citrate NF (TEC) was supplied by Morflex Inc. (Greensboro, NC). Talc USP (Imperial 500) was donated by Luzenac America, Inc. (Centennial, CO). Polyethylene glycol (PEG) 3350 NF and hydroxypropyl methylcellulose (Methocel® K4M) were supplied by The Dow Chemical Company (Midland, MI). Microcrystalline cellulose (MCC, Avicel® PH-200 and PH-101) was donated by FMC BioPolymer (Newark, DE). Polyvinylpyrrolidone K-30 (PVP, Kollidon® 30) was supplied by BASF Corp. (Mt. Olive, NJ). Colloidal silicon dioxide (Cab-O-Sil® M-5P) was donated by Cabot Corporation (Billerica, MA).

5.3 METHODS

5.3.1 Coating powder preparation

Eudragit® L 100-55 and Eudragit® RL PO were pre-plasticized by hot melt extrusion using the method described by Zheng et al. for mixtures of Eudragit® RS and Eudragit® RL PO [5]. The process was later adapted for the pre-plasticization of Eudragit® L 100-55 [6]. Prior to extrusion, both Eudragit® L 100-55 and Eudragit® RL PO were combined with TEC in a high shear mixer (RSI 3VG, Robot Coupe Scientific-Industrial Division, Joliet, IL). For the extrusion of Eudragit® L 100-55 containing 30% TEC based on the polymer weight, the temperature zones of the single screw extruder (Randcastle Model RC 0750, Cedar Grove, NJ) were set to: zone 1 = 80ºC, zone 2 = 110ºC, zone 3 = 115ºC, die = 120ºC. Eudragit® RL PO with a TEC content of 10% based on the polymer weight was extruded at slightly different temperatures: zone 1 = 80ºC, zone 2 = 105ºC, zone 3 = 115ºC, die = 125ºC. For both extrusion processes, a cylindrical die with an inner diameter of 6mm was used. A Randcastle RCP-2.0 pelletizer was employed to cut the extrudate into pellets which were subsequently ground into a fine powder using a cryogenic milling process (CF Mikro-Bantam Cryogenic Grinder, Micron Powder Systems, Summit, NJ). The ground extrudate was sieved by mechanical shaking for 15 minutes to exclude the particle size fractions below 200 and above 100 mesh (below 75 μm and above 150 μm respectively) as recommended in previous publications [5, 6].

5.3.2 Tablet preparation

Sodium valproate (15%), Avicel® PH-200 (81.25%), and Kollidon® 30 (3%) were blended in a Yoke V-shape blender (Patterson-Kelley Co., East Stroudsburg, PA) for 15 minutes. The formulation was mixed for an additional 5 minutes after the addition of the magnesium stearate (0.5%) and colloidal silicon dioxide (0.25%). Tablets with a weight of 74.8 ± 0.3 mg (n = 6, standard deviation) were directly compressed on a single stage press (Stokes F press, Bristol, PA) using deep concave 5 mm punches. A breaking load of 74.5 ± 5.3 N (n = 6, standard deviation) was measured using a WTP-3 tablet tester (Heberlein &. Co. AG, Wattwil, Switzerland). The disintegration time was determined to be 22 min, according to USP 29 using a USP Disintegration Tester (Vankel Industries Inc., Chatham, NJ).

5.3.3 Powder coating process

A modified laboratory scale spheronizer (Model 120, G.B. Caleva, Dorset, UK) was used for powder coating of 40 g batches of tablets, as previously described in the literature [4-6]. The processing conditions varied according to the coating formulation and are presented in Table 5.1. Eudragit® E PO and Eudragit® RL PO were employed as subcoating materials, while Eudragit® L 100-55 was used as the enteric polymer. The temperature of the coating bed was monitored using a Fluke 61 Infrared Thermometer (Fluke Corporation, Everett, WA). Talc was added as an anti-tack agent at 10% of the ground extrudate weight. The addition of talc considerably affected the adhesion of

Eudragit® E PO onto the tablet cores and was thus excluded in formulations of this polymer. Methocel® K4M and PEG 3350 were each added to the coating powder as pore forming agents at 10% of the ground extrudate weight. It was necessary to adjust the feeding rate of the coating powder onto the tablets cores according to the ability of the coating powder to adhere, which decreased with increasing coating levels. Following the application of the molten primer PEG 3350, the polymer mixture adhered well and was therefore applied onto the tablet cores at a feeding rate of about 3 g/min until a polymer weight gain of 5% was obtained. The powder feeding rate was then reduced to approximately 0.5 g/min. Eudragit® E PO formulations did not require a primer and the coating powder was fed at a rate of approximately 0.5 g/min throughout the process. Since all coating formulations exhibited poor flow properties, the powder mixtures were manually fed onto the tablet surfaces. After completion of the coating process, tablets were subsequently cured either in the operating spheronizer or in a static oven on Teflon trays. To prevent sticking during storage at 25ºC/60% RH and 40ºC/75% RH, the cured tablets were over-coated with 2% talc based on the weight of the coated tablets in the spheronizer.

5.3.4 Film preparation

Powder cast films were prepared by placing the ground extrudate into Teflon coated aluminum dishes with a Teflon coated lid. The Eudragit® L 100-55 films were stored in a static oven at 80ºC for 3 hours and 24 hours at 60ºC to simulate the coating and the curing process. Eudragit® E PO and Eudragit® RL PO films required higher

curing temperatures and were cured at 80ºC for 24 hours also in a static oven. A compression force of 9.8 N was applied on 22 cm^2 of film during the curing process to facilitate polymer particle fusion and to reduce the formation of voids in the film.

5.3.5 Drug release study and quantitative TEC analysis

The dissolution test was performed according to the USP Drug Release Standard for Enteric Coated Articles Method A which was recently proven to generate results that are comparable with data that were obtained using Method B [17]. Following dissolution in 750 mL 0.1N HCl for two hours, 250 mL of 0.2M tribasic sodium phosphate solution were added to the dissolution vessel. After the dissolution medium was adjusted to pH 6.8 ± 0.05, the test was continued for 2 additional hours. The dissolution media were maintained at 37 °C and agitated at 50 rpm using a USP 29 Apparatus 2 (Vankel VK 7000; Vankel Industries Inc., Cary, NC). Six tablets were placed into each of either three or six dissolution vessels respectively (n = 3 x 6 tablets/vessel or n = 6 x 6 tablets/vessel). Samples were withdrawn by an autosampler over the 4 hour period (Vankel VK 8000; Vankel Industries Inc., Cary, NC). All samples were filtered using 0.45 μm nylon filters. A HPLC system with a photodiode array detector (Model 996, Waters, Milford, MA) at a wavelength of 210 nm was employed to analyze the sodium valproate concentration in the dissolution samples. The HPLC method was adapted from a method described by Bruce et al. [8]. The 50 μL samples were injected using an autosampler (Model 717plus). Data collection and analysis were performed using Empower® Version 5.0 software. A Phenomenex Luna C18(2), 3 μm, 150 mm × 4.6 mm column (Phenomenex

Inc., Torrance, CA) was used at a column temperature of 30 ± 2ºC. The mobile phase contained a mixture of sodium phosphate monobasic and acetonitrile in a volume ratio of 63:37. The pH of the mobile phase was adjusted to 2.3 using phosphoric acid. A flow rate of 1 mL/min resulted in a retention time of 18 min for sodium valproate. Linearity was demonstrated from 4 to 100 μg/mL ($R^2 > 0.999$).

The TEC content of the coating powder and powder cast films was determined with the same equipment used in the quantitative analysis of sodium valproate according to a method previously described in the literature at a detection wavelength of 210 nm [6]. 500 mg of the coating powder or powder cast films were dissolved in 50 mM pH 7.4 buffer and then diluted 1:2 with 50 mM pH 2.5 phosphate buffer to precipitate the polymer ($n = 3$). The samples were then filtered using 0.2 μm nylon filters to remove the polymer from solution. The injection volume was set to 50 μL. An ODS-3 3 μm, 150 mm × 4.6 mm column (Alltech Inertsil™, Deerfield, IL, USA) was employed at a column temperature of 30 ± 2ºC. The mobile phase contained a mixture of acetonitrile and pH 2.5 10 mM phosphate buffer in a volume ratio of 55:45. The flow rate of 1 mL/min resulted in a retention time of 4.0 min for TEC. Linearity was demonstrated in the concentration range of 100 to 500 μg/mL ($R^2 > 0.999$).

5.3.6 Differential scanning calorimetry

Modulated differential scanning calorimetry (MDSC) was employed to investigate the thermal properties of polymeric films and melt extrudates using a Thermal Advantage Model 2920 (TA Instruments, New Castle, DE) equipped with Universal

Analysis 2000 software. The samples were sealed in aluminum pans (Kit 0219-0041, Perkin-Elmer Instruments, Norwalk, CT). The flow rate of the ultrahigh pure nitrogen purge gas was 150 ml/min. The temperature ramp rate was set to 3°C/min to characterize the interactions occurring between subcoat and enteric coat or 5°C/min at a modulation rate of ±1.00°C every 60 seconds to study the thermal properties of the subcoating materials containing pore formers. The inflection glass transition temperatures (T_g) were determined using the reverse heat flow of the second heating cycle. The heat of fusion (Q_f) was determined by linear peak integration from 40 to 70ºC. The first heating cycle was used for PEG 3350, the second heating cycle was used for the powder-cast polymer films.

5.3.7 Mechanical testing

The mechanical testing of powder-cast Eudragit® L 100-55 films containing 10% PEG 3350 based on the ground extrudate was performed using a puncture test that was adapted from a method previously described by Bodmeier et al. [18]. A Chatillon Universal Tension / Compression Tester Model TCD-200 (Ametek, Largo, FL) was used with a DFGS 50 digital force gauge to determine the puncture strength and elongation of powder-cast polymer films as a function of storage time. The film specimen was mounted onto the open mouth of a film holder that consisted of an aluminum cup with an inner diameter of 15 mm and an upper mounting plate. The puncture probe (length, 31mm; diameter, 6mm; dome shaped probe end) was lowered toward the center of the film specimen at a crosshead speed of 10 mm/min. The load (N) and deflection (mm) at

maximum were used to determine the maximum puncture strength (MPa) and % elongation (puncture strength = F/A_{cs}, where F is the load and A_{cs} is the cross-sectional area in the path of the cylindrical opening; % elongation = $[\{(R^2 + D^2)^{1/2} - R\}/R]\cdot 100$, where R is the radius of the film and D is the deflection of the probe). SPSS Version 15.0 was used for the statistical analysis of the data.

5.3.8 Scanning electron microscopy

Scanning electron microscopy (SEM) was used to examine the morphology of the surface of powder-cast films and tablet cores at 10 kV and 20 mA (Model S-4500 FE, Hitachi, London UK). The samples were sputter coated with platinum/palladium (80:20) using a Cressington Sputter Coater 208 HR equipped with a Thickness Controller MTM 20 (Cressington Scientific Instruments Ltd., Watford, UK) at 20 mA until a coating thickness of 15 nm was obtained.

5.3.9 ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy and fourier transform infrared spectroscopy

^{1}H and ^{13}C Nuclear magnetic resonance spectroscopy (^{1}H and ^{13}C NMR) as well as Fourier transform infrared spectroscopy (FTIR) were performed to investigate possible interactions between sodium valproate and PEG 3350 after heating at 80ºC for 3 hours followed by 24 hours at 60ºC to simulate the temperatures occurring during the coating and curing processes. For NMR analysis, 10 mg of sample was dissolved in deuterium

dioxide containing 3-(trimethylsilyl)-propionic acid-D4, sodium salt (TSP) as the internal standard. The NMR spectra were obtained using a Varian Inova 500 (Varian Inc., Palo Alto, CA). Prior to FTIR analysis, the single components and the heat-treated physical mixture were compressed with potassium bromide into pellets under vacuum using a compression pressure of 10 tons. A Nicolet Magna IR-560 FT-IR spectrometer was used to acquire the transmittance spectra of the materials.

5.4 RESULTS AND DISCUSSION

5.4.1 Surface properties of sodium valproate tablets

Interfacial properties of polymeric coating materials and the substrate surface such as interfacial tension and wetting have been described as key factors for polymer adhesion [19]. Obara and coworkers demonstrated that the addition of acetylated monoglycerides to the plasticizer significantly improved coating powder adhesion compared to the plasticizer alone due to a reduced contact angle for the polymer [1]. Zheng et al. reported that the application of a molten layer of cetyl alcohol enhanced the adhesion of pre-plasticized Eudragit® RS / RL PO mixtures onto the surface of theophylline tablets [5]. A PEG 3350 primer and the additional incorporation of PEG 3350 into the coating powder formulation as a low melting, hydrophilic material was necessary to facilitate adhesion of pre-plastiziced Eudragit® L 100-55 [6].

In the current study, the coating process used for chlorpheniramine maleate (CPM) tablets with pre-plasticized Eudragit® L 100-55 [6] was unsuccessful due to insufficient sticking of the enteric polymer to the sodium valproate tablets. Poor adhesion of pre-plasticized Eudragit® L 100-55 in the current study was initially thought to be due to less efficient spreading of the molten PEG 3350 primer over microcrystalline cellulose (MCC) compared to more hydrophilic diluents such as lactose. Upon further study, it was shown that coating powder can be successfully applied to CPM tablets containing solely MCC as filler, proving MCC is not limiting adhesion (data not shown). Additional SEM studies demonstrated that tablets containing high MCC levels were characterized with smoother surfaces compared to lactose containing cores (data not shown). Surface roughness is an important factor for particle adhesion. Smooth surfaces generally improve adhesion due to increased molecular attractions [20].

To exclude the possibility of chemical binding of PEG 3350 and sodium valproate at elevated temperatures, ^{1}H and ^{13}C NMR as well as FTIR spectroscopy were performed. Both NMR and FTIR spectra of the single components and the annealed physical mixture were identical with no detectable new peaks or peak shifts occurring (data not shown). Consequently binding interactions of PEG 3350 and sodium valproate were not considered as a cause for the poor coating powder adhesion.

5.4.2 Prediction of interaction parameters based on solubility parameters

The spreading of the PEG 3350 priming layer over the tablet cores was described to be crucial in the powder coating process [6]. Solubility parameters of materials have

been used to predict cohesive and adhesive properties of APIs and pharmaceutical excipients. The method which is based on the Lennard-Jones pair potential function was initially introduced for pharmaceutical applications by Rowe [21]. In the simplified model, hydrogen bonding forces were combined with polar forces to form polar components of the solubility parameter. The interaction parameter (Φ) was calculated using the harmonic mean equation derived by Wu [22] to determine the relative strength of interaction (σ).

The Hoftyzer, van Krevelen 3D solubility parameters and the corresponding interaction parameter for theophylline, CPM, valproic acid, and PEG 3350 are presented in Table 5.2. The solubility parameter of valproic acid was used in the calculations since it is not possible to calculate the solubility parameters of salts using the group contribution method. According to Rowe, the adhesive strength between materials A and B needs to be larger than the cohesive strength of interaction of B in order to facilitate spreading of substance B over substance A. The calculated values in Table 5.2 suggest that the spreading of PEG 3350 over dosage forms containing valproic acid is not favored, whereas CPM and theophylline promote spreading of the priming agent. The latter two APIs have been previously used in dry powder applications [6].

5.4.3 Powder coating process

In a method previously used to powder coat with Eudragit® L 100-55, PEG 3350 was incorporated into the coating powder [6]. In this study, to overcome adhesion difficulties, the pre-plasticized Eudragit® L 100-55 and PEG 3350 were fed separately

onto the sodium valproate containing tablet cores. A modified spheronizer was used for the process as previously described [4-6]. First, a PEG 3350 priming layer was applied onto the tablet cores with a weight gain of 3% based on the tablet weight. Then the pre-plasticized Eudragit® L 100-55 was blended with talc as an anti-tack agent and fed onto the tablet cores at a rate of approximately 3 g/min in alternation with PEG 3350. The advantage of this modified dry powder coating technique is the high powder feeding rate throughout the coating process.

The drug release profiles of powder-coated tablets that were prepared using the modified method are presented in Figure 5.1. A high level of enteric polymer was required to prevent drug release in acidic media. Polymer weight gains up to 20% resulted in a drug release of more than 10% after two hours in gastric conditions. A polymer weight gain of 28% Eudragit® L 100-55 delayed drug release in acid and allowed a fast release pH 6.8 buffer. The PEG 3350 level in the film coating for the 10, 15, 20, and 28% polymer weight gain were approximately 41, 39, 32, and 26% based on the weight of the ground pre-plasticized Eudragit® L 100-55, respectively, compared to 10% that was used in the previous study for CPM tablets [6]. The PEG 3350 content decreased in the polymer film with increasing coating levels due to an increased capacity for the Eudragit® L 100-55/talc mixture to adhere. The high PEG 3350 levels resulted in an increased hydrophilicity of the polymer film. The elevated water permeability of the enteric coat required high polymer weight gains to control the drug release.

5.4.4 Storage stability of powder-coated tablets

The physical stability of the powder-coated tablets (28% polymer weight gain) was investigated during storage at either 25ºC/60% RH or 40ºC/75% RH for 12 weeks. After curing for 6 hours in the spheronizer at 60ºC and 170 rpm, an overcoat of 2% talc, based on the final tablet weight, was applied onto the tumbling tablets. The tablets were sealed in HDPE containers with desiccant. Prior to dissolution testing, all samples were equilibrated in the sealed container at ambient conditions for 24 hours. The drug release profiles of the enteric-coated sodium valproate tablets are presented in Figure 5.2. The powder-coated tablets exhibited excellent storage stability at 25ºC/60% RH with no detectable changes in drug release. In contrast, drug release decreased and became less consistent with a higher standard deviation over time when stored at 40ºC/75% RH.

PEG 3350 is a known plasticizer for Eudragit® L 100-55, therefore, while it functions as a primer, it would also further plasticize the coating polymer during storage. DSC analysis revealed that the T_g of pre-plasticized Eudragit® L 100-55 containing an additional 25% PEG decreased to 13.9±3.8ºC (standard deviation, n = 3). The low T_g of the coating formulation was connected with a high molecular mobility of the polymer that resulted in physical instability of the film coating.

5.4.5 Properties of subcoated sodium valproate tablets

In order to avoid large PEG 3350 levels in the Eudragit® L 100-55 coating, different subcoating materials were investigated. Eudragit® E PO and Eudragit® RL PO

were chosen as potential subcoating materials since both polymers were successfully used in previous dry-powder coating applications [4, 5]. Due to their solubility properties, both polymers would delay drug release in pH 6.8 buffer, a characteristic that is not desired for enteric coated dosage forms. Consequently, pore forming agents were added to the subcoating to increase water influx and hence drug dissolution in the buffer stage of the enteric test. Methocel® K4M and PEG 3350 were chosen as possible pore formers.

In Figure 5.3, the drug release profiles of sodium valproate tablets powder-coated with either Eudragit® E PO (A) or pre-plasticized Eudragit® RL PO (B) are presented. Both acrylic polymers were used alone and in combination with PEG 3350 and Methocel® K4M in a 10:1 ratio. A 10:2 ratio was also tested, but did not show any advantages compared to the lower pore forming content. The investigated polymer weight gains included 5 and 10% for subcoating formulations containing PEG 3350. The maximum weight gain for subcoating formulations containing Methocel® K4M did not exceed 7% due to insufficient coating powder adhesion. The aim was to obtain a drug release of over 90% after 45 minutes in pH 6.8 50mM buffer as a benchmark to ensure that the subcoating material did not delay drug release in the buffer phase. The objective was met with a 5% weight gain of Eudragit® E PO, Eudragit® E PO in combination with PEG 3350, or Eudragit® RL PO in combination with Methocel® K4M. Both PEG 3350 and Methocel® K4M demonstrated pore forming activity for Eudragit® E PO. Cerea et al. previously demonstrated that the addition of hydrophilic polymers to the coating formulation increased the drug release of tablets that were powder-coated with Eudragit® E PO in pH 6.8 50mM phosphate buffer [4].

The pore forming effect of Methocel® K4M in powder-layered Eudragit® RL PO films was stronger than the one of PEG 3350. At high coating levels, PEG 3350 reduced the drug release when compared with tablets that were powder-coated with Eudragit® RL PO without added pore forming agents. Similar results were obtained by Lippold et al. who described a decrease in the drug release from theophylline pellets that were coated with Eudragit® RS containing 10% PEG compared to a Eudragit® RS coating formulation without pore former or with a 10% admixture of HPMC [23].

To better understand the influence of pore forming agents on the release of sodium valproate, polymer films were powder cast, cured, and the properties were investigated using dissolution testing, SEM, and DSC. The SEM micrographs of free films before and after 30 min in pH 6.8 buffer are presented in Figure 5.4. Both the incorporation of PEG 3350 and Methocel® K4M into Eudragit® E PO films resulted in pore formation after dissolution in pH 6.8 buffer. Since PEG 3350 has a melting point below the processing temperature, PEG 3350 containing films were characterized by numerous small pores while the dissolution of Methocel® K4M generated large openings within the Eudragit® E PO film. In contrast, the addition of PEG 3350 to Eudragit® RL PO did not produce any visible pores after 30 minutes in the dissolution media (pH 6.8 buffer). Only the combination of Eudragit® RL PO with Methocel® K4M resulted in pore formation after exposure to dissolution media. The SEM results correlated well with the dissolution data. Miscibility and compatibility of coating excipients with the functional polymer were shown to influence the permeability of film coatings [24].

To further investigate the miscibility of the pore forming agents in the film matrix, the powder-cast films were analyzed using DSC. Eudragit® E PO did not show

miscibility with both PEG 3350 and Methocel® K4M. As a result, both materials act as pore former when combined with the polymer. The DSC profiles of the Eudragit® E PO films containing PEG 3350 showed a large endothermic peak due to the melting of the pore former (Figure 5.5). The melting peak of PEG 3350 was broadened and slightly shifted from 60.5 ± 0.3ºC (standard deviation, n = 3) for bulk PEG 3350 to 55.3 ± 0.2ºC (standard deviation, n = 3) when incorporated into Eudragit® E PO. Q_f of PEG 3350 was slightly decreased (160.6 ± 5.8 J/g, standard deviation, n = 3) compared to Q_f of bulk PEG 3350 that was determined to be 196.6 ± 24.4 J/g (standard deviation, n = 3). PEG 3350 and Methocel® K4M did not produce a significant change in T_g of Eudragit® E PO (45.4 ± 2.0ºC, standard deviation, n = 3). Also the T_g of Methocel® K4M (179.5 ± 2.9ºC, standard deviation, n = 3) was not significantly influenced when combined with Eudragit® E PO.

In combination with Eudragit® RL PO, PEG 3350 demonstrated partial miscibility or was present in an amorphous state in the polymer film (Figure 5.5). The melting point of PEG 3350 was shifted to 50.7 ± 1.2ºC (standard deviation, n = 3). Q_f of PEG 3350 in the polymer films was reduced to 10.0 ± 4.8 J/g (standard deviation, n = 3). The T_g of Eudragit® RL PO (pre-plasticized with 10% TEC based on the polymer weight) was slightly decreased from 42.1 ± 0.1ºC (standard deviation, n = 3) for the bulk polymer to 33.6 ± 5.9ºC (standard deviation, n = 3) when combined with PEG 3350. The miscibility of PEG 3350 in the acrylic polymer affected its function as pore former and improved film formation. DSC thermograms of Eudragit® RL PO films that contained Methocel® K4M showed two T_g and thus no miscibility. The T_g of Methocel® K4M did not change significantly whereas the T_g of Eudragit® RL PO increased to 50.2 ± 1.8ºC (standard

deviation, $n = 3$) due to possible interactions of the plasticizer TEC with the hydrophilic pore former.

5.4.6 Properties of sub- and enteric-coated sodium valproate tablets

Three subcoating formulations at a 5% coating level were chosen for further investigation in an enteric powder-coating process: Eudragit® E PO without a pore former, Eudragit® E PO containing PEG 3350, and pre-plasticized Eudragit® RL PO in combination with Methocel® K4M. The selection criterion was a sodium valproate release of more than 90% in pH 6.8 buffer after 45 minutes of dissolution.

In Figure 5.6, the drug release profiles of sodium valproate tablets subcoated and subsequently enterically coated using a dry-powder coating technique are presented. All Eudragit® E PO subcoated tablets were cured in a static oven at 80ºC for 12 hours, while Eudragit® RL PO subcoated tablets were cured in the revolving spheronizer at 60ºC for 2 hours prior to application of the enteric polymer. Curing of the Eudragit® E PO tablets in the spheronizer was not possible due to chipping of the functional coating. The Eudragit® L 100-55 film coating was applied using the same technique previously developed for the coating of CPM tablets [6]. The process involved the use of pre-plasticized (30% TEC) Eudragit® L 100-55 in combination with a PEG 3350 primer and the incorporation of a small amount of PEG 3350 into the coating formulation. The enteric-coated tablets were subsequently cured in the rotating spheronizer for 6 hours.

A coating level of 20% Eudragit® L 100-55 was employed to control the drug release for all formulations. Both the Eudragit® E PO subcoating formulation with PEG

3350 and the Eudragit® RL PO composition with Methocel® K4M resulted in a delay of sodium valproate release in acid and a fast release in buffer. Both formulations passed the USP requirements for enteric coated tablets when overcoated with adequate levels of Eudragit® L 100-55. A Eudragit® E PO subcoat without the incorporation of a pore forming agent, Figure 5.6 (A), did not provide a rapid drug release during the buffer stage of the enteric test, because of the polymer's insolubility in alkaline media. Additional curing after application of the enteric film coating and potential plasticizer migration from the pre-plasticized Eudragit® L 100-55 to the Eudragit® E PO improved subcoat film formation. As a result, the release in buffer was further delayed.

5.4.7 Stability of sub- and enteric-coated sodium valproate tablets

The physical stability of the sub- and enteric-coated sodium valproate tablets was investigated over 12 weeks at either 25ºC/60% RH or 40ºC/75% RH. Two different subcoating materials were investigated: Eudragit E PO containing PEG 3350 in a 10:1 ratio and Eudragit® RL PO containing Methocel® K4M in a 10:1 ratio. All investigated tablets were subcoated to a polymer weight gain of 5% and enteric-coated to a polymer weight gain of 20%. The tablets were cured in the revolving spheronizer for 6 hours before they were overcoated with 2% talc based on the weight of the coated tablets and sealed in HDPE containers with desiccant. Both formulations demonstrated excellent storage stability at 25ºC/60% RH over 12 weeks. The drug release of the Eudragit® E PO subcoat formulation decreased continuously at 40ºC/75% RH over 12 weeks while the

drug release of the Eudragit® RL PO subcoat formulation stabilized after four weeks (Figure 5.7).

Important factors that affect the storage stability of coated dosage forms are plasticizer content and change in the mechanical properties of the polymeric films. The TEC content in the coating powder and in powder-cast films initially and after 4 and 12 weeks is presented in Table 5.3. Free Eudragit® L 100-55 films containing 30% TEC based on the polymer weight were either stored at 25ºC/60% RH or at 40ºC/75% RH in sealed HDPE containers with desiccant to determine the plasticizer loss. The TEC content in the polymeric films did not change significantly at 25ºC/60% RH. There was a significant decrease in TEC concentration (ANOVA, Tukey's HSD, $p<0.05$) after storage at 40ºC/75% RH for 4 and 12 weeks. The elongation of powder-cast films increased over storage and was significant after 12 weeks of storage compared to the initial value for both storage temperatures at 0% RH (ANOVA, Tukey's HSD, $p<0.05$). However, there was no significant difference in elongation between storage at 25ºC compared to storage at 40ºC after 12 weeks. The puncture strength did not change significantly at 25ºC/0%RH and 40ºC/0%RH over the investigated storage time (ANOVA, Tukey's HSD, $p<0.05$).

Another theory included the aging of the subcoating layer and interactions occurring between subcoat and enteric coating. This hypothesis agreed with a previous study that investigated the physico-chemical stability of tablets that were powder-coated using pre-plasticized Eudragit® L 100-55 without prior application of subcoat [6]. The drug release fluctuated slightly around the initial profile, but did not drastically decrease over storage. Increased molecular mobility at high storage temperatures and additional plasticization by PEG 3350 were the suggested rationale [6].

DSC was employed to investigate interactions between Eudragit® E PO and pre-plasticized Eudragit® L 100-55. The thermogram of a physical mixture of bulk Eudragit® E PO and pre-plasticized Eudragit® L 100-55 containing 30% TEC was characterized by two T_g, one at 24.9 ± 0.9ºC (standard deviation, n = 3) and one at 73.6 ± 7.7ºC (standard deviation, n = 3), as presented in Figure 5.8. In contrast, the T_g of bulk Eudragit® E PO was 43.5 ± 0.8 ºC (standard deviation, n = 3), and that of pre-plasticized Eudragit® L 100-55 containing 30% TEC was determined to be 61.3 ± 3.1ºC [6]. DSC analysis revealed that the T_g of Eudragit® E PO was lowered by approximately 20ºC, while the transition of Eudragit® L 100-55 was increased by approximately 10ºC. The same phenomenon was observed for physical mixtures of Eudragit® RL PO pre-plasticized with 10% TEC and Eudragit® L 100-55 pre-plasticized with 30% TEC. The DSC profile of Eudragit® RL PO containing 10% TEC was characterized by a glass transition at 44.3 ± 2.4 ºC (standard deviation, n = 3). The DSC profile showed two T_g: one for Eudragit® RL PO at 29.5 ± 4.0ºC and one at 72.0 ± 3.5ºC for Eudragit® L 100-55. This corresponds to a shift of approximately 10ºC down for Eudragit® RL PO and 10ºC up for Eudragit® L100-55 compared to the pre-plasticized bulk polymers. TEC can therefore migrate from the subcoat into the enteric coating layer at elevated temperatures, as demonstrated with the TEC loss over storage and change the physico-chemical properties of the powder-coated tablets. This phenomenon was more pronounced for the unplasticized Eudragit® E PO.

5.5 CONCLUSION

Sodium valproate tablets required high weight gains of powder-coated Eudragit® L 100-55 in order to pass the USP enteric test. The application of a Eudragit® E PO or Eudragit® RL PO subcoat assisted with adhesion of the enteric polymer onto the tablet cores, enhanced film formation, and therefore reduced the amount of enteric polymer required for enteric protection. High polymer weight gains of Eudragit® L 100-55, however, were still required for the tablets to pass the USP enteric test. PEG 3350 and Methocel® K4M were added to the subcoat to improve the release of sodium valproate in buffered media. Drug release was dependent on miscibility of the pore forming agents with the polymers. Storage stability was confirmed for powder-coated sodium valproate tablets at 25ºC/60% RH for all investigated formulations. Storage at 40ºC/75% RH resulted in fluctuations in sodium valproate release over 12 weeks. A Eudragit® RL PO subcoat resulted in the smallest change in the drug release over the storage period. A loss of plasticizer in the enteric film coating was shown to affect the storage stability of the powder-coated sodium valproate tablets.

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5.7 TABLES AND FIGURES

Table 5.1: Processing parameters and formulations for the powder-coating of sodium valproate tablets.

	Formulation	Primer	Coating additives	Coating temperature	Rotation speed
Eudragit® L 100-55	A	3% PEG^{++}	10% talc^{+}	70-75ºC	220 rpm
	B		10% talc^{+} 10% PEG^{+}		
Eudragit® E PO	C	N/A	N/A	55-60ºC	170 rpm
	D		10% PEG^{+}		
	E		10% K4M^{+}		
Eudragit® RL PO	F	3% PEG^{++}	10% talc^{+}	60-65ºC	220 rpm
	G		10% talc^{+} 10% PEG^{+}		
	H		10% talc^{+} 10% K4M^{+}		

+ based on the weight of the ground extrudate; ++ weight gain, based on tablet weight

Table 5.2: Hoftyzer, van Krevelen 3D solubility parameters and interaction parameters of theophylline, chlorpheniramine maleate (CPM), valproic acid, and PEG 3350.

	PEG3350	Valproic acid	CPM	Theophylline
Hoftyzer, van Krevelen 3D solubility parameter $(J/cm^3)^{0.5}$				
D	17.4	17.1	20.8	24.6
P	1.2	2.8	3.8	16.2
H bonding	9.3	8.1	8.8	13.6
V_m (cm^3/mol)	2803.4	152.3	309.4	109.1
sol parameter (δ)	19.8	19.1	22.9	32.4
Φ with PEG		0.6	0.9	0.9
Strength of interaction J/cm^3 (σ)				
Cohesive (PEG)	98.3	98.3	98.3	98.3
Adhesive (A-B)		59.2	102.9	152.7

Table 5.3: 12 week stability of powder-cast films of Eudragit® L 100-55 pre-plasticized with 30% TEC containing 10% PEG 3350 (standard deviation, *n* = 3).

		TEC recovery [%]	Puncture strength	Elongation [%]
Coating powder		100.4±0.3 %	N/A	N/A
Initial		100.1±0.3 %	1.18±0.16 MPa	112.6±9.6 %
4 weeks	25ºC	99.4±0.3 %	1.04±0.28 MPa	140.3±24.9 %
	40ºC	97.2±0.7 %*	1.20±0.18 MPa	130.7±16.4 %
12 weeks	25ºC	98.9±0.1 %	0.90±0.10 MPa	164.0±23.0 %*
	40ºC	95.3±1.0 %*	1.05±0.21 MPa	160.8±27.5 %*

* Denotes statistical significant difference to initial value (ANOVA, Tukey's HSD, $p<0.05$).

Figure 5.1: Influence of coating level on the release of sodium valproate from tablets powder-coated with pre-plasticized Eudragit® L 100-55 using USP 29 apparatus 2. Dissolution in 750mL of 0.1N HCl for 2 hours followed by 2 hours in 1000mL pH 6.8 50mM phosphate buffer after pH adjustment at 37ºC and 50 rpm. ■: 10% polymer weight gain. ♦: 15% polymer weight gain. ▲: 20% polymer weight gain. □: 28% polymer weight gain. (Standard deviation, n = 6 x 6 tablets/vessel.)

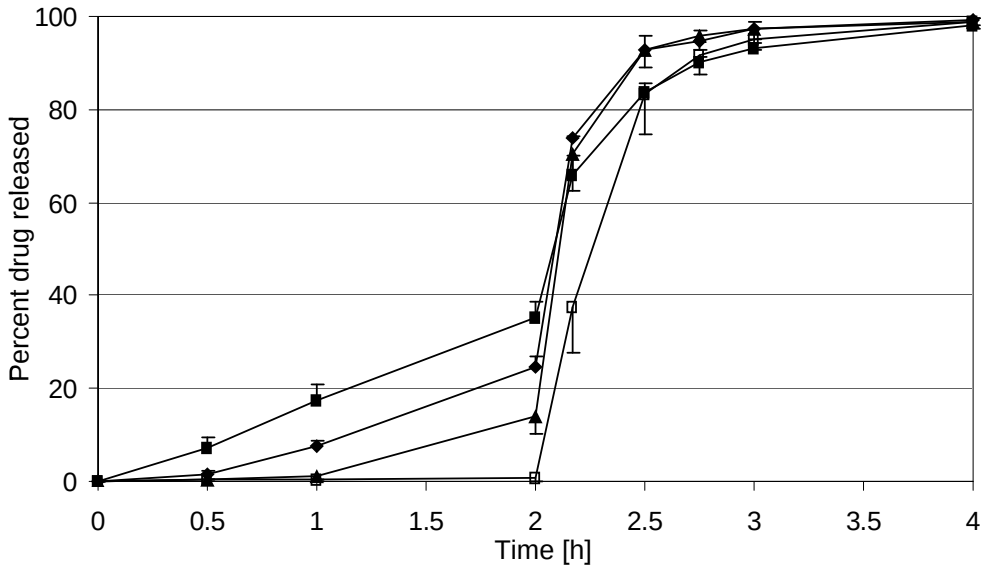


Figure 5.2: 12 week stability of sodium valproate tablets powder-coated with pre-plasticized Eudragit® L 100-55 containing 30% TEC based on the polymer weight using USP 29 apparatus 2. Dissolution in 750mL of 0.1N HCl for 2 hours followed by 2 hours in 1000mL pH 6.8 50mM phosphate buffer after pH adjustment at 37ºC and 50 rpm. Polymer weight gain: 28%. ■: initial. ♦: 4 weeks at 25ºC / 60% RH. ▲: 4 weeks at 40ºC / 75% RH. □: 12 weeks at 25ºC / 60% RH. ◊: 12 weeks at 40ºC / 75% RH. (Standard deviation, n = 6 x 6 tablets/vessel.)

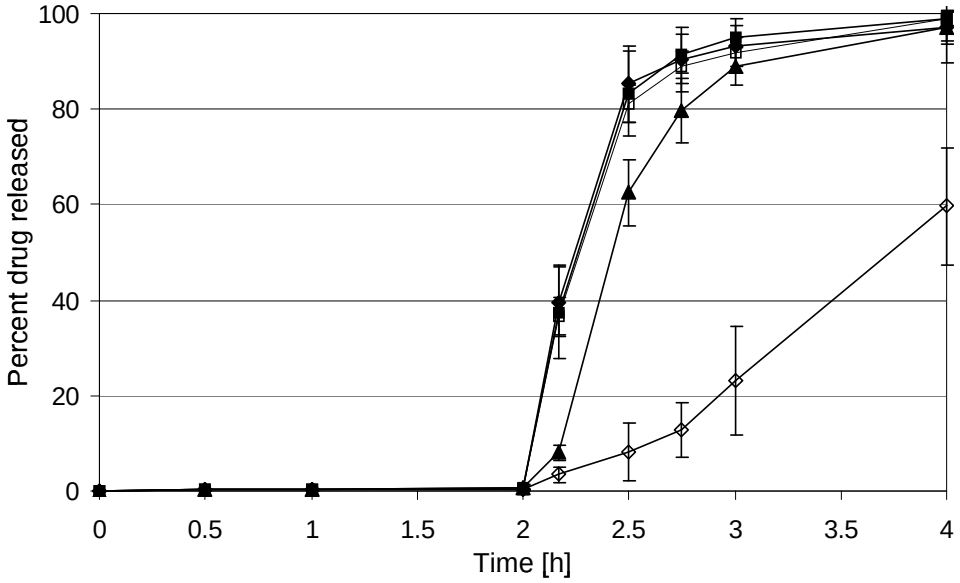
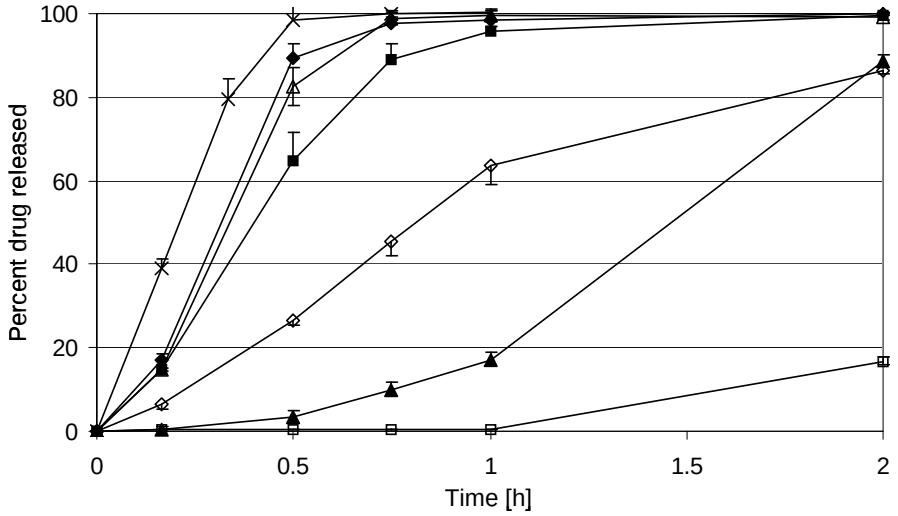


Figure 5.3: Influence of polymer weight gain (PWG) and pore formers on the release of sodium valproate from powder-coated tablets using USP 29 apparatus 2. Dissolution in 900mL pH 6.8 50mM phosphate buffer at 37ºC and 50 rpm. ×: core tablets. ♦: polymer / PEG 3350 ratio 10:1, 5% PWG. ▲: polymer / PEG 3350 ratio 10:1, 10% PWG. ■: polymer / Methocel® K4M ratio 10:1, 5% PWG. ◊: polymer / Methocel® K4M ratio 10:1, 7% PWG. Δ: no pore former, 5% PWG. □: no pore former, 10% PWG. (A) Eudragit® E PO. (B) Eudragit® RL PO plasticized with 10% TEC. (Standard deviation, n = 6 x 6 tablets/vessel.)



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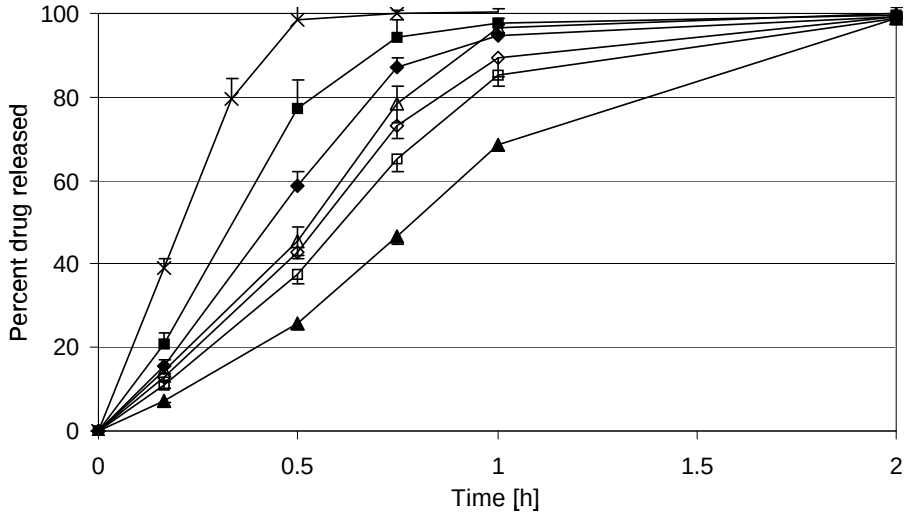


(B)

Figure 5.4: Surface morphology of powder cast polymer films before (A-D) and after dissolution in pH 6.8 buffer for 30 minutes (E-H). A and E: Eudragit® E PO / PEG 3350, ratio 10:1. B and F: Eudragit® E PO / Methocel® K4M, ratio 10:1. C and G: Eudragit® RL PO / PEG 3350, ratio 10:1. D and H: Eudragit® RL PO / Methocel® K4M, ratio 10:1.

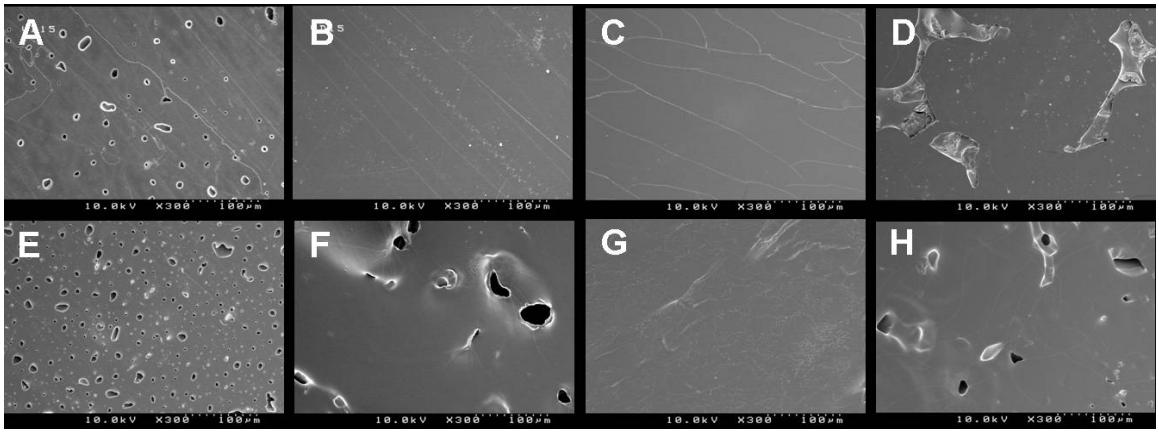


Figure 5.5: DSC thermograms of Eudragit® E PO and Eudragit® RL PO, pre-plasticized with 10% TEC based on the polymer weight containing either PEG 3350 or Methocel® K4M in a 10:1 ratio.

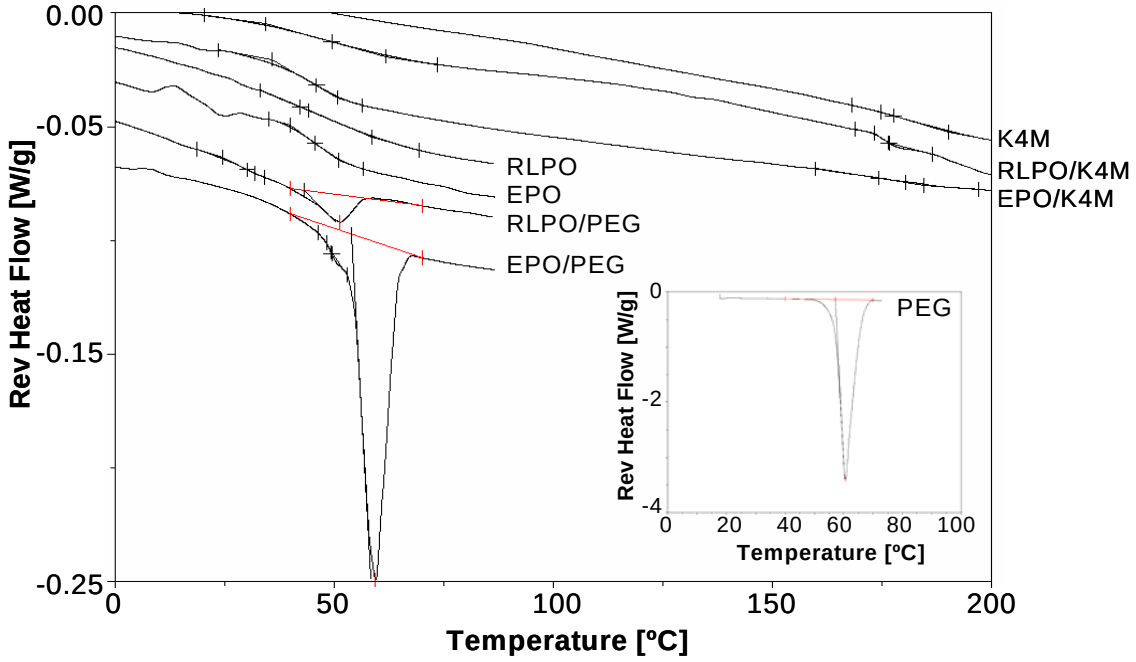
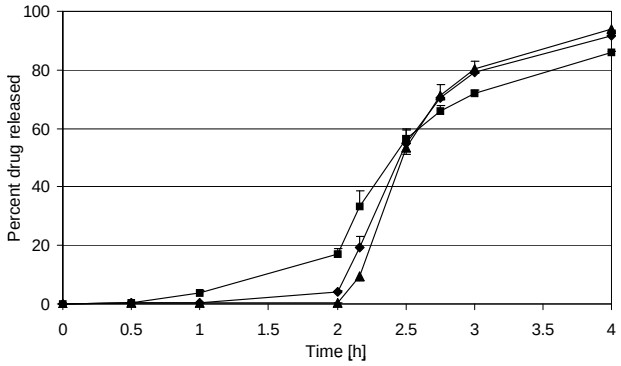


Figure 5.6: Influence of coating level on the release of sodium valproate from tablets powder-coated with pre-plasticized Eudragit® L 100-55 using USP 29 apparatus 2. Dissolution in 750mL of 0.1N HCl for 2 hours followed by 2 hours in 1000mL pH 6.8 50mM phosphate buffer after pH adjustment at 37ºC and 50 rpm. ■: 10% polymer weight gain. ♦: 15% polymer weight gain. ▲: 20% polymer weight gain. (Standard deviation, n = 6 x 6 tablets/vessel.) (A) 5% Eudragit® E PO subcoat, no pore former. (B) 5% Eudragit® E PO subcoat containing 10% PEG 3350 based on the polymer weight. (C) 5% Eudragit® RL PO subcoat containing 10% Methocel® K4M based on the polymer weight.



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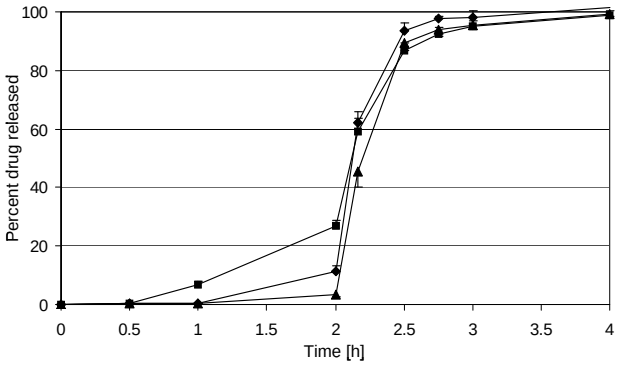

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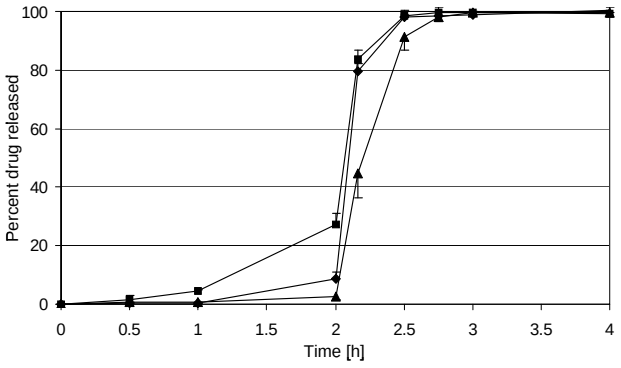
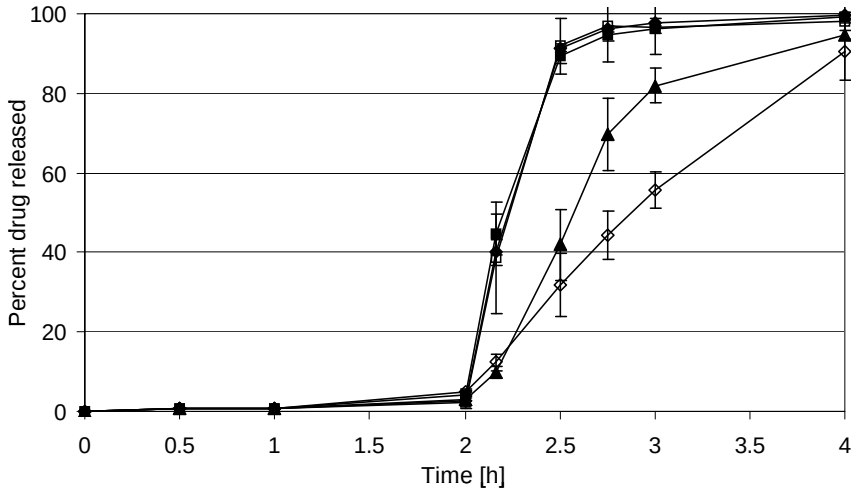


(C)

Figure 5.7: 12 week stability of sodium valproate tablets powder-coated with pre-plasticized Eudragit® L 100-55 containing 30% TEC based on the polymer weight using USP 29 apparatus 2. Dissolution in 750mL of 0.1N HCl for 2 hours followed by 2 hours in 1000mL pH 6.8 50mM phosphate buffer after pH adjustment at 37ºC and 50 rpm. Polymer weight gain: 28%. ■: initial. ♦: 4 weeks at 25ºC / 60% RH. ▲: 4 weeks at 40ºC / 75% RH. □: 12 weeks at 25ºC / 60% RH. ◊: 12 weeks at 40ºC / 75% RH. (Standard deviation, n = 6 x 6 tablets/vessel.) (A) Eudragit® E PO subcoat containing 10% PEG 3350 based on the polymer weight. (B) Eudragit® RL PO subcoat containing 10% Methocel® K4M based on the polymer weight.



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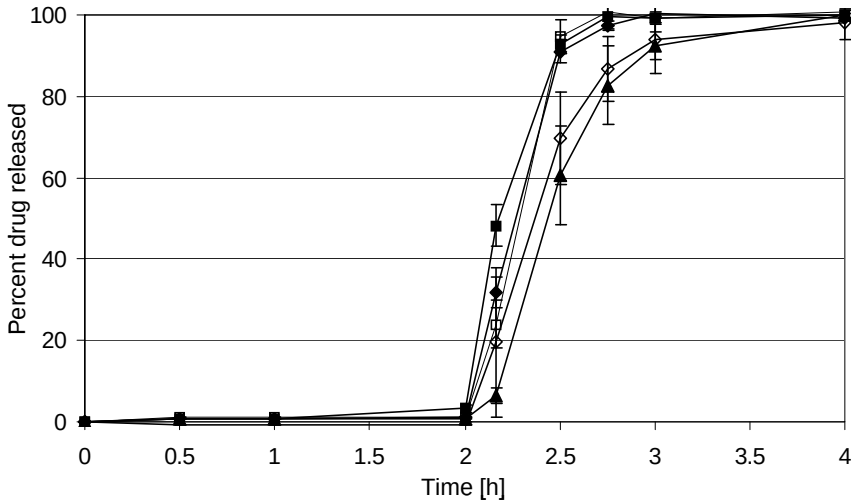
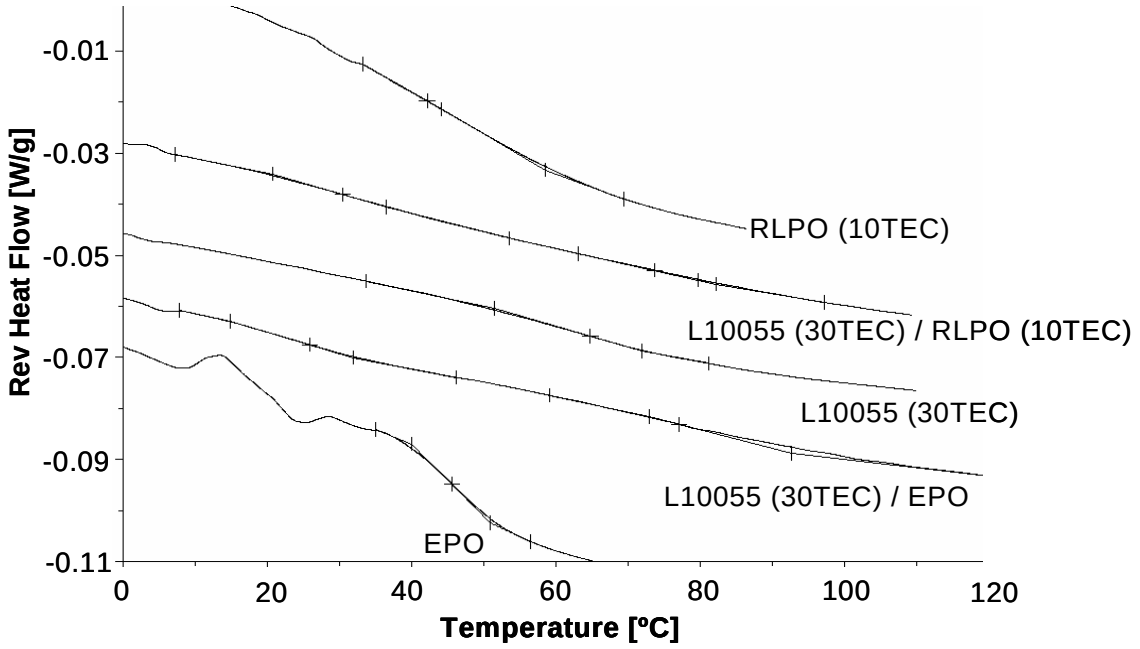


(B)

Figure 5.8: DSC thermograms of Eudragit® L 100-55, pre-plasticized with 30% TEC, Eudragit® E PO, and Eudragit® RL PO, pre-plasticized with 10% TEC and their 1:1 physical mixtures.



Chapter 6: Study of the Influence of Additives on Melt Viscosity, Surface Tension, and Film Formation of Dry Powder Coatings[2]

Abstract:

The aim of this study was to characterize the film formation process of thermally cured Eudragit® L 100-55 dry-powder coatings. The main focus was to investigate the influence of film additives on melt viscosity and surface tension, the main parameters that influence polymer particle fusion and surface leveling of the polymeric film. The coating process employed no liquids and the plasticizer was combined with the polymer using hot melt extrusion. Thermogravimetric analysis confirmed thermal stability of all coating excipients at the investigated curing conditions. The influence of the level of triethyl citrate (TEC) as plasticizer and polyethylene glycol (PEG) 3350 in the polymer film on film formation was investigated. The rheological behavior of the coating formulations were characterized with the extrusion torque, and the surface energy parameters were determined from contact angle measurements. Increasing TEC levels and the addition of PEG 3350 as a low melting excipient in the coating reduced the viscosity of the polymer. In contrast, plasticization of the polymer with TEC increased the surface free energy, whereas the admixture of 10% PEG 3350 did not affect the surface free energy of Eudragit® L 100-55. The spreading coefficient of the polymers over two sample tablet formulations was reduced with increasing surface free energy. During the curing process,

[2] Significant portions of this chapter were taken from: Sauer D. and J.W. McGinity. Influence of Additives on Melt Viscosity, Surface Tension, and Film Formation of Dry Powder Coatings. This paper is under review by *Drug Development and Industrial Pharmacy.*

puncture strength and elongation of powder-cast films increased. The effect of curing time on the mechanical properties was dependent on the plasticizer content.

6.1 INTRODUCTION

The mechanism of film formation occurring in dry coating processes has been described in the literature [1, 2]. However, there is little information available on the characteristics of thermally cured dry-powder coatings used for pharmaceutical solid oral dosage forms. The properties that have been used to evaluate film formation in pharmaceutical coatings included glass transition temperature and minimum film formation temperature of the polymers, dissolution data, and scanning electron micrographs [3-5]. The main parameters that influence film formation of such dry powder coatings, including melt viscosity and surface tension of the polymer have not been discussed in the pharmaceutical literature.

Huang and coworkers divided the film formation process for dry coating into four stages [2]. Initially, powders are deposited on the surface and packed together. Secondly, sintering and coalescence of the polymer particles occur. Film leveling mainly takes place during the curing process, and lastly, cooling of the film completes the process [2]. A high initial packing density of the coating powder is essential for polymer particle fusion. Johnson and coworkers introduced a model to determine the contact area between two spheres that were pressed into contact [6]. According to this theory the diameter of the contact spot was dependent on three main parameters: external force, surface

attractions, and elastic properties of the deformed particles [7]. The film forming process of powder coatings is dependent on coalescence of the polymer particles and wetting of the tablet surface [1]. The main driving force for coalescence and leveling is the surface tension of the polymer, with a low surface tension resulting in wavy surfaces and a high surface tension causing crater defects due to poor wetting properties [8]. The main resistance to fusion of polymer particles is the melt viscosity of the polymer. According to Nix and Dodge, the time needed to fuse two polymer particles increases with decreasing surface tension, as expressed in Equation 1 [9].

$$t = f(\eta R_c/\sigma) \quad (1)$$

where t is the flow time, η is the melt viscosity, R_c is the average radius of curvature, and σ is the surface tension of the polymer.

Orchard developed a model for the surface leveling in viscous liquids and gels [10] that also describes the flow of powder coatings [1]. According to this model, the rate of leveling is increased for polymers with high surface tension, low melt viscosity, small particle size and for polymeric films with high film thickness. Additives including plasticizers can affect melt viscosity as well as the surface tension of polymers. The incorporation of plasticizers was shown to significantly reduce the melt viscosity of polymers [9, 11]. The effect of additives on the surface free energy was demonstrated to be dependent on the amount and type of additive, although small amounts of dibutyl sebacate and dibutyl phthalate to ethylcellulose films did not influence the surface free energy of cast polymer films [12]. In contrast, the inclusion of different grades of PEG increased the surface free energy of Eudragit® RS films [13].

The objective of this study was to characterize the curing process of dry-powder Eudragit® L 100-55 films and to investigate the influence of the plasticizer triethyl citrate (TEC) and the coating excipient polyethylene glycol 3350 (PEG 3350) on melt viscosity, surface tension, and film formation.

6.2 MATERIALS

Eudragit® L 100-55 was donated by Evonik Industries AG (Piscataway, NJ). Triethyl citrate (TEC) was supplied by Vertellus Materials Inc. (Greensboro, NC). Polyethylene glycol (PEG) 3350 NF was purchased from the DOW Chemical Company (Midland, MI). Lactose monohydrate NF, magnesium stearate, and the model drugs chlorpheniramine maleate (CPM) and sodium valproate (SoVa) were purchased from Spectrum Chemical Mfg. Corp. (Gardena, CA). Microcrystalline cellulose (Avicel® PH-101 and PH-200) were supplied by FMC Corp. (Newark, DE). Kollidon® K 30 was donated by BASF Corp. (Mount Olive, NJ). Cab-O-Sil M-5P was supplied by Cabot Corp. (Tuscola, IL).

6.3 METHODS

6.3.1 Hot-melt extrusion

Eudragit® L 100-55 was pre-plasticized with up to 40% triethyl citrate (TEC) by melt extrusion using a Randcastle Model RC 0750 with a 6 mm die that was connected to a Randcastle Pelletizer RCP-2.0 (Randcastle Extrusion Systems, Inc., Cedar Grove, NJ). The temperature zones of the extruder were kept at 80ºC (zone 1), 110ºC (zone 2), 115ºC (zone 3), and 120ºC (die). The screw speed was set to 20 rpm and resulted in drive amps between 0.3 to 0.5 for the 20% TEC level and 0.1 to 0.2 at the TEC concentration of 40%. The extruded pellets were subsequently ground into a fine coating powder using a cryogenic mill (Model CF, Micron Powder systems, Summit, NJ) and screened using mechanical shaking. The particle size fraction between 200 and 100 mesh (75 - 150 μm) was then used in this study for dry powder coating as recommended in a previous study [4].

6.3.2 Thermal analysis

The thermal stability of the coating excipients and a powder-cast film was investigated using thermogravimetric analysis (TGA). A sample of approximately 10 mg was equilibrated to 50ºC and then heated at a rate of 10ºC/min to 800ºC. At isothermal conditions, the equilibration of the sample to 50ºC was followed by heating to 60ºC and the temperature was then kept constant for 6 hours.

6.3.3 Relative melt viscosity

The mixing torque necessary to extrude Eudragit® L 100-55 containing various amounts of TEC and PEG 3350 was determined using a Haake MiniLab-Compounder (Thermo-Fisher Scientifc Inc., Waltham, MA) in the cycle mode. The screw speed was set to 10 rpm. The temperature range was adjusted for each formulation. The maximum temperature did not exceed 125ºC to avoid side chain degradation of the polymer [14]. The torque cut off value occurred at 550 Ncm and restricted measurements at low temperature values.

6.3.4 Contact angle measurements

A Carver Laboratory Press (Model M, ISI Inc., Round Rock, TX) was used to manufacture compacts from pre-plasticized Eudragit® L 100-55, PEG 3350, and three tablet formulations at a 1000 kg compression force (Table 6.1). 3 µL of water, ethylene glycol or diiodomethane were placed onto the surface of the compacts using a microsyringe with Teflon tip. The contact angle was determined by measuring the tangent to the curve of the sessile droplet using a Goniometer (Model No. 100-00-115, Ramé-Hart Inc., Mountain Lakes, NJ) within 5 seconds after drop deposition. The measurements were performed in triplicate at 25ºC. The apolar and the acid-base components of the surface free energy were calculated according to an approach by van Oss and coworkers using the following equation [12, 15]

$$\gamma_L(1+\cos\theta) = 2(\sqrt{\gamma_S^{LW}\gamma_L^{LW}} + \sqrt{\gamma_S^{+}\gamma_L^{-}} + \sqrt{\gamma_S^{-}\gamma_L^{+}}) \quad (2)$$

where γ is the surface free energy, θ is the measured contact angle, γ^{LW} is the apolar component associated with the Lifshitz-van der Waals (LW) interactions, γ^{+} is the electron-acceptor parameter (Lewis acid) of the acid-base contributions, and γ^{-} is the electron donor parameter (Lewis base) of the acid-base contributions. The subscripts *S* and *L* distinguish between the solid and the liquid used in the experiment. The surface free energy parameters of the liquids were taken from the literature [12, 16].

6.3.5 Preparation and characterization of free films

Free films were prepared from the pre-plasticized Eudragit® L 100-55 that contained 20, 30, or 40% TEC based on the polymer weight. The polymer was blended with 10% PEG 3350 based on the weight of the ground extrudate using mortar and pestle. Prior to curing in a static oven at 60ºC, the coating powder was pressed into films using a compression force of 10 kN on a surface area of 22 cm^2 for 3 minutes to ensure a dense powder packing (Carver Laboratory Press, Model M, ISI Inc., Round Rock, TX). The compression force was reduced during the curing process to 10 N. The mechanical properties of powder-cast Eudragit® L 100-55 films were investigated using a puncture test previously described by Bodmeier et al. [17, 18]. A Chatillon Universal Tension / Compression Tester Model TCD-200 (Ametek, Largo, FL) with a DFGS 50 digital force gauge was used to study puncture strength and elongation of powder-cast polymer films after up to 12 hours of curing at 60ºC. The puncture probe (length, 31 mm; diameter, 6mm; dome shaped end) was lowered toward the center of the film specimen that was clamped into a film holder at a crosshead speed of 10 mm/min. The film holder consisted

of an open-mouth Aluminum cup with an inner diameter of 15 mm and an upper mounting plate. The load (N) and deflection (mm) at maximum was used to determine the maximum puncture strength (MPa) and % elongation at maximum (puncture strength = F/A_{cs}, where F is the load and A_{cs} is the cross-sectional area in the path of the cylindrical opening; % elongation = $[\{(R^2 + D^2)^{1/2} – R\}/R]\cdot 100$, where R is the radius of the film and D is the deflection of the probe). Statistical analysis of the data was performed using SPSS Version 15.0.

6.4 RESULTS AND DISCUSSION

6.4.1 Thermal stability

The raw materials Eudragit® L 100-55, TEC, and PEG 3350 as well as a powder cast film were subject to thermogravimetric analysis (TGA) to evaluate the thermal stability during the curing process. Two different TGA methods were evaluated. Incremental heating of the samples, as shown in Figure 6.1, demonstrated thermal stability with no signs of degradation occurring at the curing temperature 60ºC. TEC decomposed above 200ºC, whereas the polymers Eudragit® L 100-55 and PEG 3350 showed signs of degradation above 300ºC. Petereit et al. employed TGA combined with mass spectroscopy to characterize the thermal degradation process of acrylic polymers [14]. It was demonstrated that Eudragit® polymers showed a loss of functional groups

above approximately 130ºC. Reactions of the main chain such as depolymerisation or cross-linking were noted at processing temperatures above approximately 300ºC. The TGA profile of a powder-cast film exhibited weight loss in the same temperature ranges and at ratios expected based on the raw materials. The polymer film contained 30% TEC based on the polymer weight and 10% PEG 3350 based on the weight of the ground extrudate and was cured for 24 hours in a static oven at 60ºC before analysis.

Isothermal TGA analysis at 60ºC over 6 hours revealed stability of the coating excipients with minimal weight loss occurring over the investigated time frame (Table 6.2). The 6 hours time frame corresponded to the investigated curing time in this study. The weight loss of Eudragit® L 100-55 and PEG 3350 was negligible, with less than 0.2%. The highest weight loss with a value of approximately 2% was noted for TEC. In a powder cast film as described in the previous paragraph the loss of TEC would result in a combined weight loss of less than 0.5%.

6.4.2 Relative melt viscosity

Melt viscosity is considered to be the main resistance for polymer flow and polymer-particle fusion [9]. The temperature dependence can be expressed by the Arrhenius-Frenkel-Eyring equation [19]:

$$\eta = B \exp\left(\frac{E_a}{RT}\right) \quad (3)$$

where B is a polymer specific constant, E_a is the activation energy of the viscous flow, R is the gas constant, and T is the absolute temperature. The logarithm of the melt viscosity

plotted against the reciprocal value of temperature in an Arrhenius diagram results in a straight line at a constant shear rate when the activation energy is independent from temperature [20]. The surface tension is linearly temperature dependent, decreasing with increasing temperatures [8]. However, this effect is less pronounced compared to the temperature effect on melt viscosity.

Torque data have been widely used to characterize the rheological behavior of polymers under processing conditions [21-23] and to determine the relative melt viscosity of materials [24]. At constant rotor speed, the equilibrium torque was shown to be directly proportional to the apparent shear viscosity [25, 26]. The torque data for the circulation of each formulation in a twin-screw extruder were graphed in a direct plot and in an Arrhenius diagram (Figure 6.2). The plasticizer content had a strong effect on shear viscosity, with decreased viscosity noted with increasing plasticizer levels. It has been proposed that a decrease reduces the time needed for polymer-particle fusion and leveling of a polymer film [9, 10]. The incorporation of PEG 3350 into Eudragit® L 100-55 based powder coating formulations as a low melting coating excipient was previously recommended to assist with coating powder adhesion [4]. PEG 3350 is a known plasticizer for Eudragit® L 100-55 and additionally reduced the viscosity of Eudragit® L 100-55. Therefore, the inclusion of PEG 3350 was expected to have a positive effect on film formation.

All investigated formulations followed a linear relation when the natural logarithm of the torque was plotted against the reciprocal absolute temperature in the investigated temperature range. The square of the correlation coefficient (R^2) from regression analysis for Eudragit® L 100-55 containing 20, 30, or 40% TEC based on the

polymer weight was 0.943, 0.995, and 0.988 respectively. The addition of 10% PEG 3350 based on the weight of the ground extrudate to the pre-plasticized polymer resulted in R^2 values of 0.997, 0.997, and 0.977. This linear relationship can be used to predict the viscosity outside of the investigated temperature range [27]. Extrapolation to the curing temperature of 60ºC continued the trend of torque reduction with increasing plasticizer levels (data not shown).

The flow activation energy at constant shear rate can be obtained from the slope that was determined using regression analysis as described above [28]. Since only torque data were available to describe the rheological behavior of the dry powder coating formulations the slopes were compared relative to each other and no flow activation energy values were calculated. Figure 6.2 B does not show a clear trend on the slope for increasing TEC amounts in the coating formulation. The slope slightly declined for the TEC content of 30% compared to the 20% TEC ratio and increased again for the 40% TEC level. In contrast, a small decline of the slopes was observed for all TEC concentration after the addition of PEG 3350 as coating excipient and thus resulted in a small decrease of the flow activation energy.

6.4.3 Surface free energy parameters

One simple method to determine the surface free energy parameters in terms of the Lifshitz-van der Waals and acid-base contribution of multi-component systems is the analysis of contact angles with both hydrophilic and hydrophobic liquids [15]. This method has been used in pharmaceutical research to characterize adhesion between

polymer film and substrate surfaces [12, 29, 30] and wetting phenomena in a wet-granulation process [31]. Young's equation requires a smooth and homogeneous surface with no interactions or adsorption occurring in order to calculate the interfacial energy between two materials,

$$\gamma_{sv} = \gamma_{sl} + \gamma_{lv} \cos\theta \quad (4)$$

where γ is the surface tension (or surface free energy) and θ is the contact angle. The subscripts sv, sl, and lv refer to the interfaces between solid and vapor, solid and liquid, and liquid and solid, respectively. Although these assumptions are often difficult to meet in practice, contact angle studies are acknowledged for the comparative determination of surface properties of materials [12, 30]. In this study, the contact angles decreased over time, a phenomenon that has previously been described for the sessile drop method [12, 30]. Previous workers have reported that the advantage of the sessile drop method, compared to advancing contact angles, is the low prevalence of salvation, hydration, or swelling of the analyzed material, provided that the contact angle is immediately measured after deposition of the drop on the surface [30]. Oss et al. recommended the use of three different liquids of which two must be polar to determine the surface free energy parameters of surfaces [15].

The non-polar (dispersion) and polar components of the surface energy of compacts of pre-plasticized Eudragit® L 100-55, PEG 3350, and their physical mixtures are presented in Table 6.3. In a preliminary study with diiodomethane, ethylene glycol, and water all materials listed in Table 6.3 and Table 6.4 were determined to be Lewis-bases and strongly monopolar with a Lewis acid component of surface interaction (γ^+) of approximately zero (data not shown). The results correspond to literature values for the

acrylic polymer and PEG [32, 33]. Further studies were performed solely with diiodomethane and water with the assumption that γ^+ equals zero to avoid negative square roots in the calculations as already described for materials with improved adhesion behavior, such as corona or flame treated polyolefins [32]. The equation for the calculation of the Lewis base component then simplifies to [32]:

$$-2\sqrt{\gamma_L^+\gamma_S^-} = -\gamma_L(1+\cos\theta_{L/S}) + 2\sqrt{\gamma_L^{LW}\gamma_S^{LW}} \quad (5)$$

where γ is the surface free energy, θ is the measured contact angle, γ^{LW} is the apolar component associated with LW interactions, γ^+ is the electron-acceptor parameter, and γ^- is the electron donor parameter of the acid-base contributions. The subscripts *S* and *L* distinguish between the solid and the liquid used in the experiment. The surface free energy parameters of the liquids were taken from the literature [12, 16]. Contact angles of materials were shown to decrease with temperature; however, not markedly [34, 35]. Since the temperature coefficient for PEG and acrylic polymers is less than 0.1 $mJ/m^2/K$ [33], the interfacial energies were determined at 25ºC as approximation although the coating temperature and curing temperature were 70-75ºC and 60ºC, respectively. No contact angle data could be obtained for compacts made from Eudragit® L 100-55 with a TEC content of 40%. At this high plasticizer concentration the contact angles decreased rapidly both for diiodomethane and water.

The surface free energy can be calculated from the surface free energy parameters using the following equation [15]:

$$\gamma_{TOT} = \gamma^{LW} + 2(\sqrt{\gamma^+\gamma^-}) \quad (6)$$

where γ^{LW} is the apolar Lifshitz-van der Waals parameter. γ^+ and γ^- are the Lewis-acid and Lewis-base component of the surface free energy, respectively which describe electron donor/acceptor interactions. Since all materials from Table 6.3 were determined to be monopolar Lewis-bases, the surface free energy equaled the Lifshitz-van der Waals parameter. The surface free energy of Eudragit® L 100-55 increased with increasing TEC content. In contrast, the addition of PEG 3350 to the coating formulation did not show any influence on the surface free energy of the polymer, although PEG 3350 resulted in an increase of the Lewis-base component of the surface free energy.

The spreading coefficient of material A over material B can be determined using the following equation [12, 36]:

$$S = \gamma_B - \gamma_A - \gamma_{AB} > 0 \tag{7}$$

where γ is the surface free energy. The interfacial energy γ_{AB} between two materials was calculated according to the following equation [15]:

$$\gamma_{AB} = (\sqrt{\gamma_A^{LW}} - \sqrt{\gamma_B^{LW}})^2 + 2(\sqrt{\gamma_A^+ \gamma_A^-} + \sqrt{\gamma_B^+ \gamma_B^-} - \sqrt{\gamma_A^+ \gamma_B^-} - \sqrt{\gamma_A^- \gamma_B^+}) \tag{8}$$

where γ^{LW} is the apolar component, γ^+ is the electron-acceptor, and γ^- is the electron donor parameter. Since γ^+ was set to zero, the interfacial energies were based on the Lifshitz-van der Waals (LW) interactions. The interfacial energy is the free energy change in expanding the interfacial area between two materials [36]. The interfacial energies between PEG 3350, three tablet formulations and various Eudragit® L 100-55 powder coating formulations are presented in Table 6.4. Since PEG 3350 had a low interfacial energy with pre-plasticized Eudragit® L 100-55, which decreased with increasing TEC levels, PEG 3350 was an effective priming material and has been used as

low melting coating excipient for the powder-coating with pre-plasticized Eudragit® L 100-55.

The chlorpheniramine maleate and sodium valproate formulations were chosen since they have been used previous in dry coating studies with Eudragit® L 100-55 [4]. The contact angles for water and diiodomethane were 21.3 ± 1.5º and 48.7 ± 1.2º for chlopheniramine maleate tablets (formulation 1), 40.0 ± 3.6º and 60.3 ± 1.2º for chlopheniramine maleate tablets (formulation 2), and 41.3 ± 2.1º and 69.3 ± 1.5 for sodium valproate tablets (formulation 3). These contact angles resulted in γ_{LW} and γ- values of 35 mJ/m^2 and 71 mJ/m^2 for chlorpheniramine maleate tablets (formulation 1), 28 mJ/m^2 and 61 mJ/m^2 for chlorpheniramine maleate tablets (formulation 2), and 23 mJ/m^2 and 67 mJ/m^2 for sodium valproate tablets (formulation 3). The interfacial energy between the tablet formulations and pre-plasticized Eudragit® L 100-55 increased with increasing TEC levels and thus affected spreading over the investigated tablet formulations, whereas PEG 3350 did not have a strong impact (Table 6.4). Using the interfacial energies the spreading coefficients of PEG 3350 and pre-plasticized Eudragit® L100-55 over the tablet cores were determined and the results are presented in Figure 6.3. The spreading coefficients of PEG 3350 over tablet formulation 1 through 3 were -12 mJ/m^2, -20 mJ/m^2, and -27 mJ/m^2, respectively. Positive spreading coefficients result in spreading of one material over the other. In this study, most spreading coefficients are negative but it should be noted that only Lifshitz-van der Waals interactions were considered in the model. The calculated spreading coefficients for the sodium valproate tablets are highly negative and therefore more difficult to compensate with other aspects of adhesion compared to the chlorpheniramine maleate tablets. Tablet formulation 1 and

2 differ in the filler composition. Tablets with higher microcrystalline cellulose content were characterized by a lower spreading coefficient compared to tablets containing lactose monohydrate in the formulation.

6.4.4 Mechanical properties

After powder deposition and packing, sintering, coalescence, and film leveling occur during the curing process of dry-powder coatings [2]. In this study the progress of film formation and extent of polymer particle fusion was studied using a puncture test on free films and the results are shown in Figure 6.4. The data were then analyzed using a One-way ANOVA followed by Tukey's HSD ($p<0.05$) of all possible paired comparisons and the results are presented in Table 6.5. The glass transition temperature of Eudragit® L 100-55 pre-plasticized with 20 to 40% TEC has been previously shown to be below the curing temperature of 60ºC and thus in a rubbery state for all TEC levels after admixture of PEG 3350 [4]. The powder-cast films were characterized by an initial maximum load of less than 0.6 N which corresponded to a puncture strength of less than 0.1 MPa for all investigated plasticizer levels (data not shown). Eudragit® L 100-55 films containing TEC concentrations of 30% and 40% based on the polymer weight were characterized by an increase of puncture strength over time, whereas it did not change for films containing 20%, as shown in Figure 6.4. The puncture strength plateaued after 6 hours of curing while the elongation continuously increased over 24 hours. The elongation increased for all TEC levels. It has been demonstrated that increasing plasticizer levels result in an increase in elongation of polymer films but a decrease in

tensile strength and elastic modulus [37, 38]. Interestingly, both the elongation and the puncture strength of the Eudragit® L 100-55 dry-powder films increased with increasing TEC levels over a curing time of 12 hours. Plasticizer molecules that are embedded in a polymer matrix generally reduce interactions between polymer chains and number of entanglements, and hence increase the flexibility and decrease the mechanical strength of polymer films. The increase in puncture strength for powder-cast films with rising TEC levels over 12 hours hence demonstrated that polymer particle fusion and film formation progressed faster at high plasticizer content, as proposed by Nix and Dodge [9].

6.5 CONCLUSION

The thermal characterization of the curing process revealed stability of the components at the investigated curing conditions. Both viscosity and surface free energy of Eudragit® L 100-55 coating formulations were shown to be a function of the TEC content. The plasticizer reduced the viscosity and increased the surface free energy of the polymer. Both low viscosity and high surface free energy were previously shown to accelerate polymer particle fusion in dry coating processes. The addition of PEG 3350 can improve film formation due to an additional reduction of viscosity. PEG 3350 did not affect the surface free energy of Eudragit® L 100-55. Mechanical testing of powder-cast films showed an increase of both elongation and puncture strength over the curing process as criterion for polymer particle fusion, where film formation progressed faster at high plasticizer levels.

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6.7 TABLES AND FIGURES

Table 6.1: Tablet formulations.

	Formulation 1	**Formulation 2**	**Formulation 3**
Model drug	CPM	CPM	Sodium valproate
	15%	15%	15%
Avicel® PH-101	46.25%		
Avicel® PH-200		81.25%	81.25%
Lactose monohydrate	35%		
Kollidon® 30	3%	3%	3%
Magnesium stearate	0.5%	0.5%	0.5%
Cab-O-Sil	0.25%	0.25%	0.25%

Table 6.2: Cumulative percent weight loss of Eudragit® L 100-55, PEG 3350, and TEC after isothermal TGA analysis at 60ºC for 6 hours.

Material	Eudragit® L 100-55	TEC	PEG 3350
Weight loss after 6 hours at 60ºC	0.13%	2.19%	0.07%

Table 6.3: Influence of plasticizer content and the addition of PEG 3350 on the surface free energy parameters of Eudragit® L 100-55 that were determined using contact angle measurements (standard deviation, $n = 3$).

		Contact angles for liquids (°)		**Surface free energy parameters (mJ/m²)**		
		Water	Diiodomethane	γ^+	γ^-	γ^{LW}
PEG 3350		22.0±2.6	24.3±2.1	0	58	46
Eudragit® L 100-55	0 TEC (bulk)	63.0±3.6	50.0±1.0	0	26	34
	20 TEC	58.7±1.2	31.0±1.0	0	23	44
	30 TEC	58.7±2.1	26.0±2.0	0	22	46
	0 TEC/10PEG	60.3±1.2	48.7±1.5	0	28	35
	20 TEC/10PEG	49.0±1.5	29.0±1.0	0	33	45
	30 TEC/10PEG	21.3±1.5	16.7±1.5	0	56	49

Table 6.4: Interfacial energies (γ) between PEG 3350 and Eudragit® L 100-55 containing various amounts of TEC and PEG 3350 as well as between PEG 3350, Eudragit® L 100-55 and two model tablet formulations.

		PEG 3350	**CPM tablets (Formulation 1)**	**CPM tablets (Formulation 2)**	**SoVa tablets (Formulation 3)**
Polymer (P)		$\gamma_{P\text{-}PEG}$ (mJ/m^2)	$\gamma_{P\text{-}CPM}$ (mJ/m^2)	$\gamma_{P\text{-}CPM}$ (mJ/m^2)	$\gamma_{P\text{-}SoVa}$ (mJ/m^2)
PEG 3350		0	1	2	4
Eudragit® L 100-55	0 TEC (bulk)	1	0	0	1
	20 TEC	0	1	2	3
	30 TEC	0	1	2	4
	0 TEC/ 10PEG	1	0	0	1
	20 TEC/ 10PEG	0	1	2	4
	30 TEC/ 10PEG	0	1	3	5

Table 6.5: Results of Tukey's HSD post hoc test ($p<0.05$) for mechanical properties of Eudragit® L 100-55 powder-cast films with 20, 30, or 40% TEC after 3, 6, 12, and 24 hours of curing at 60ºC.

		20TEC				**30TEC**				**40TEC**			
		3h	6h	12h	24h	3h	6h	12h	24h	3h	6h	12h	24h
20TEC	3h	-							*		*	*	*
	6h	**	-						*		*	*	*
	12h	**	**	-					*		*	*	*
	24h			**	-				*		*	*	*
30TEC	3h			**		-			*		*	*	*
	6h			**			-		*		*	*	*
	12h					**		-	*				*
	24h								-	*	*	*	
40TEC	3h			**						-			*
	6h	**	**		**	**	**			**	-		
	12h	**	**	**	**	**	**	**	**	**	**	-	
	24h	**	**	**	**	**	**	**	**	**	**	**	-

** Significant difference elongation [%]. * Significant difference puncture strength [MPa].

Figure 6.1: Thermal stability of Eudragit® L 100-55, PEG 3350, and TEC.

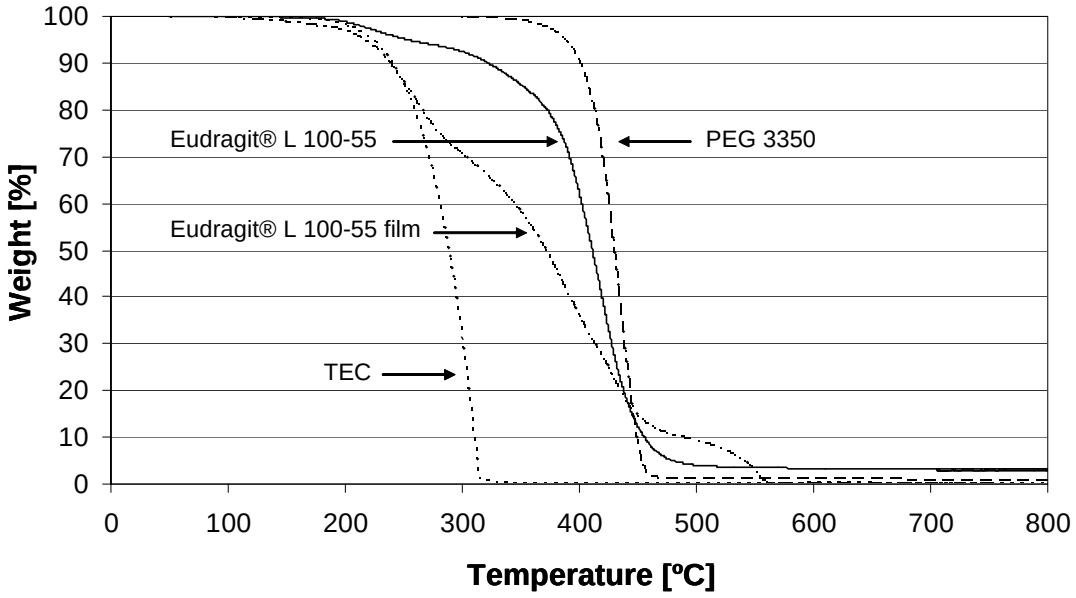
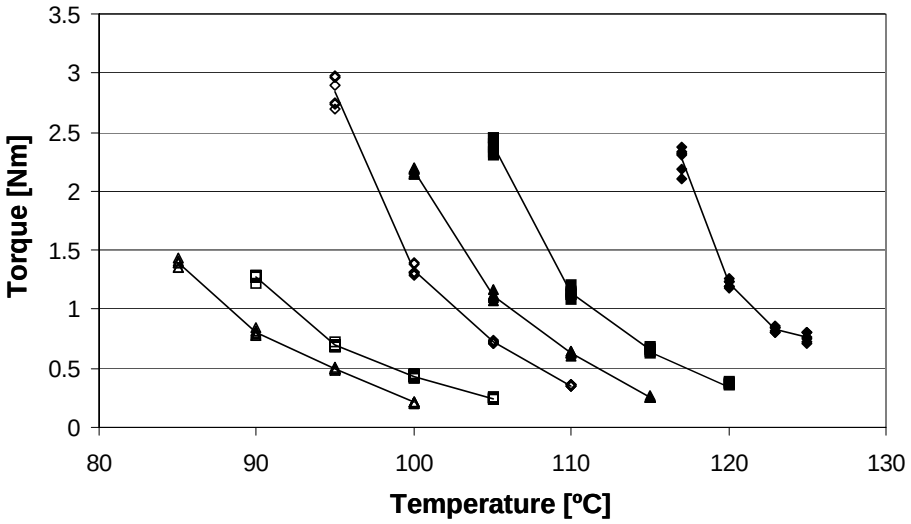
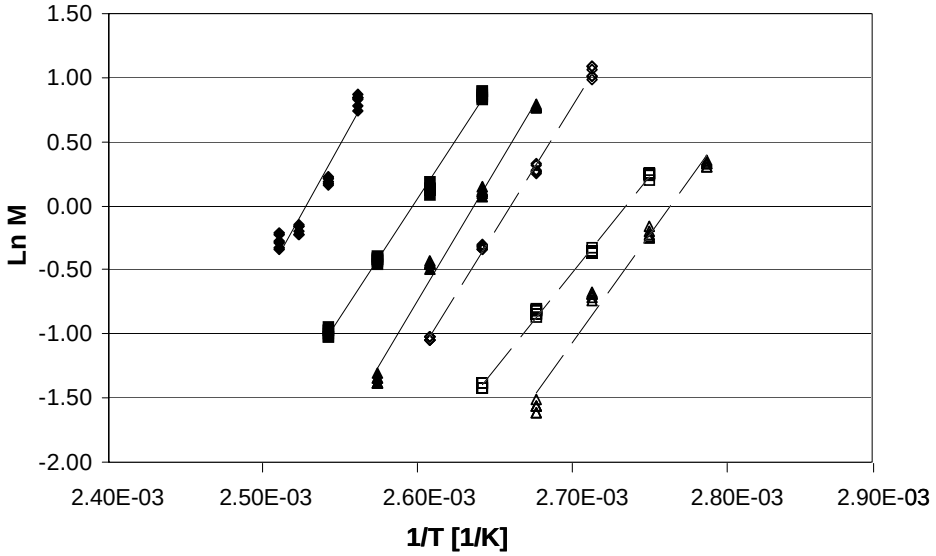


Figure 6.2: Influence of plasticizer content and the addition of 10% PEG 3350 based on the weight of the ground extrudate on the shear viscosity of Eudragit® L 100-55. ♦ Eudragit® L 100-55 containing 20% TEC. ■ Eudragit® L 100-55 containing 30% TEC. ▲ Eudragit® L 100-55 containing 40% TEC. ◊ Eudragit® L 100-55 containing 20% TEC and PEG. □ Eudragit® L 100-55 containing 30% TEC and PEG. Δ Eudragit® L 100-55 containing 40% TEC and PEG. The TEC content was based on the polymer weight. A: Direct plot. B: Arrhenius plot.



(A)



(B)

Figure 6.3: Spreading coefficients for Eudragit® L 100-55 containing different levels of TEC. ■: PEG 3350 over Eudragit® L 100-55. □ PEG 3350 over Eudragit® L 100-55 containing 10% PEG 3350. ▲: Eudragit® L 100-55 over CPM tablets (Formulation 1). Δ: Eudragit® L 100-55 containing 10% PEG 3350 over CPM tablets (Formulation 1). x: Eudragit® L 100-55 over CPM tablets (Formulation 2). -: Eudragit® L 100-55 containing 10% PEG 3350 over CPM tablets (Formulation 2). ♦: Eudragit® L 100-55 over sodium valproate tablets (Formulation 3). ◊: Eudragit® L 100-55 containing 10% PEG 3350 over sodium valproate tablets (Formulation 3).

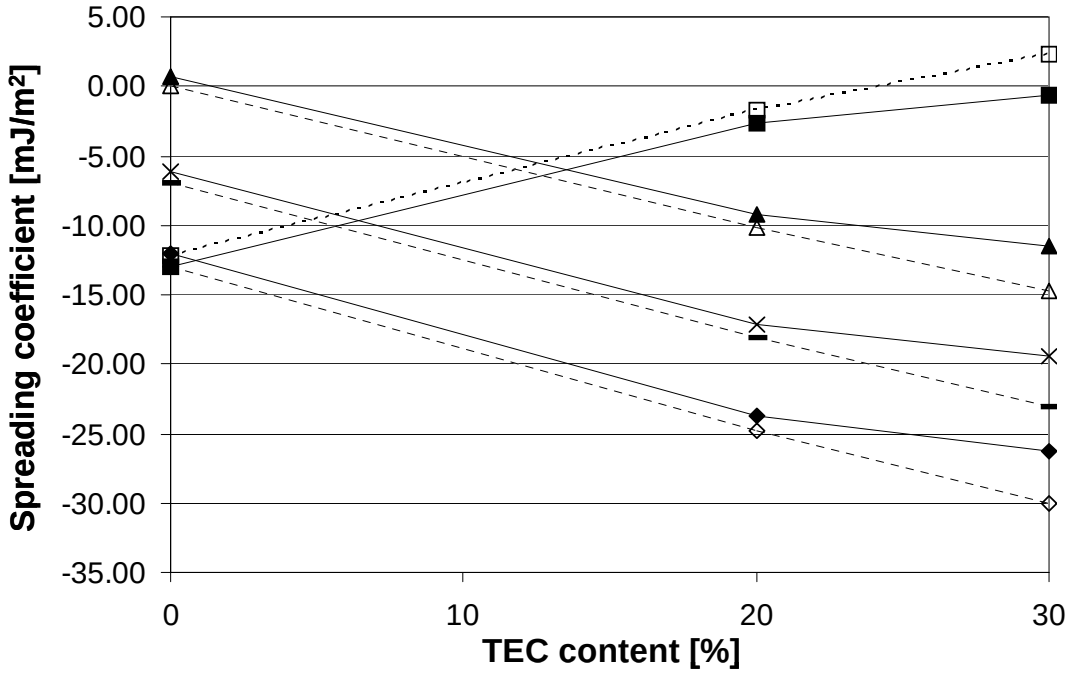
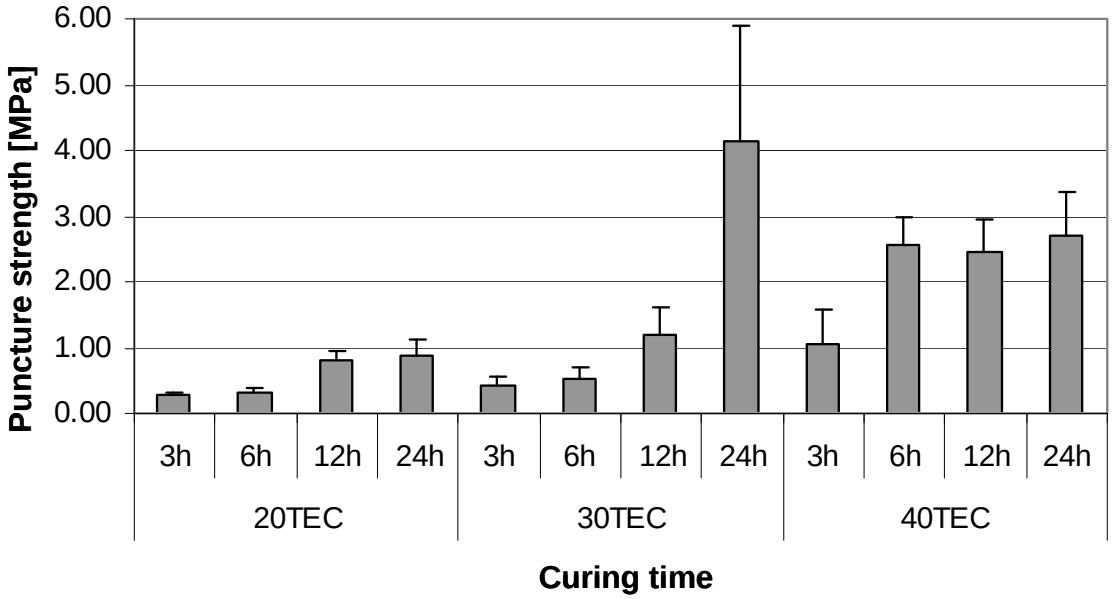
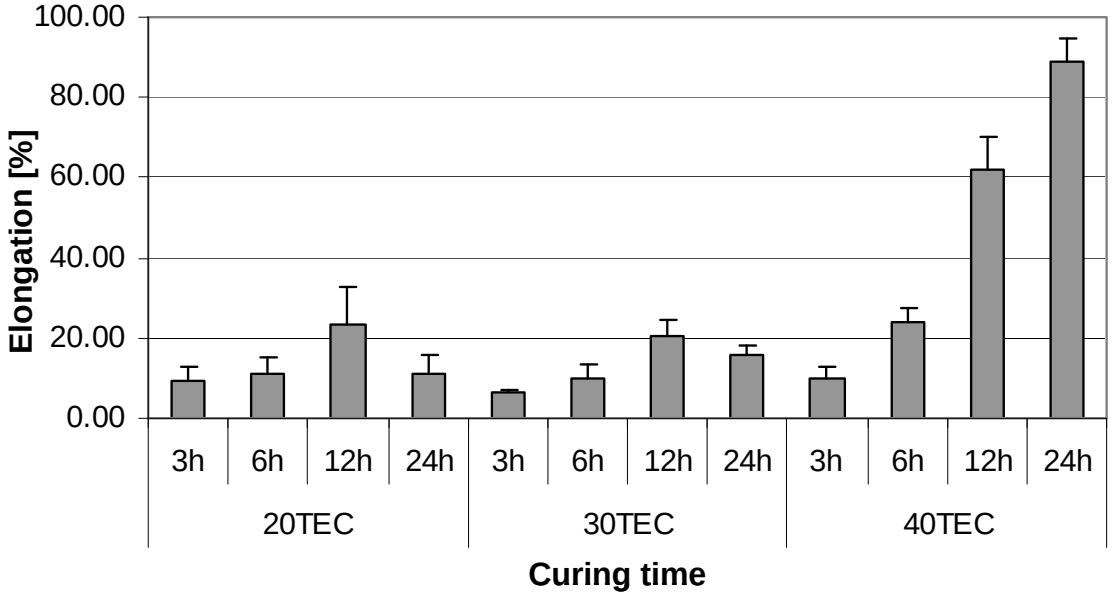


Figure 6.4: Influence of curing time at 60ºC on the puncture strength and elongation of powder-cast films from pre-plasticized Eudragit® L 100-55 (standard deviation, $n = 3$).



(A)



(B)

Chapter 7: Characterize the Properties of Theophylline Tablets Dry Powder Coated with Eudragit® E PO and Eudragit® L 100-55

Abstract:

The aim of the present study was to investigate the influence of Eudragit® E PO in Eudragit® L 100-55 film coatings applied to theophylline tablets by a dry powder coating technique on the drug release mechanism. The process was entirely liquid-free. Calculation of the Flory-Huggins interaction parameter based on solubility parameters suggested immiscibility of the copolymers. MDSC thermograms were characterized by two glass transitions for the investigated Eudragit® E PO/Eudragit® L 100-55 ratios and confirmed immiscibility of the copolymers at processing conditions. FT-IR analysis was employed to study binding interactions of the polymers. Due to the higher affinity of the plasticizer, triethyl citrate, for Eudragit® E PO compared to Eudragit® L 100-55, redistribution of the plasticizer was observed during the curing phase of the process. Plasticizer migration also affected the initial phase of drug release from powder-coated theophylline tablets that were stored for 4 weeks. The particle size of the coating powder influenced the microstructure of the film coating. Drug release from powder-coated tablets was dependent on the polymer blend ratio, coating thickness, and the pH of the dissolution medium. A broad range of pH dependent theophylline release profiles were obtained as a function of the polymer blend ratio.

7.1 INTRODUCTION

Polymer blends have been widely used in liquid based coating applications to adjust the drug release rate, to improve processing [1] and to enhance the physical stability of coated dosage forms upon storage. The presence of Eudragit® L 100-55 in Eudragit® RS 30 D film coatings was demonstrated to stabilize the drug release rate from theophylline pellets [2]. Eudragit® NE 30 D film coatings that contained Eudragit® L 30 D-55 were shown to prevent agglomeration of coated pellets during processing and upon storage [3]. The increase of the glass transition temperature in the presence of Eudragit® L 30 D-55 compared to Eudragit® NE 30 D alone was reported as the mechanism of stabilization. The addition of polymers that are immiscible with the film forming polymer were also shown to stabilize polymeric film coatings by prevention of further coalescence of the film forming polymer [4]. The combination of polymers that are used for sustained release coatings such as ethylcellulose, Eudragit® NE 30 D or Eudragit® RS with enteric polymers including Eudragit® L 100-55 and Eudragit® L 30 D-55, have been widely investigated to compensate for pH dependent solubility of active ingredients [1, 5]. Sustained release film coatings became more permeable following dissolution of the enteric polymer after passage from the stomach. Generally, it has been reported that the drug release kinetics was altered as a function of the mixing ratio of the two polymers due to changes in the permeability of film coatings [4, 5].

Eudragit® E PO/Eudragit® L 100-55 coprecipitates have been investigated for sustained drug release applications [6]. The cationic polymer Eudragit® E PO contains dimethylaminoethyl methacrylate and neutral methacrylic esters. The anionic copolymer

Eudragit® L 100-55 is based on methacrylic acid and ethyl acrylate. The ratio of free carboxyl groups to ester groups is approximately 1:1. Eudragit® E PO is soluble up to pH 5.0 and swellable and permeable above pH 5.5 whereas Eudragit® L 100-55 is only soluble above pH 5.5 in aqueous media due to ionization of the carboxylic groups. Moustafine et al. characterized Eudragit® E PO/Eudragit® L 100-55 coprecipitates as interpolyelectrolyte complexes [6]. Such complexes contain interacting chains as well as defects of non-interacting chains which affect swelling behavior and drug release. Turbidimetry, viscosity measurements, and elementary analysis demonstrated that in aqueous solution, at pH 5.5, the binding ratio was approximately 1:1. FT-IR analysis revealed that ionic bonding was the primary binding force. Matrix tablets were prepared from the physical mixture and coprecipitate of Eudragit® E PO and Eudragit® L 100-55. Tablets prepared from the physical mixture disintegrated quickly, whereas matrixes of interpolyelectrolyte complexes were characterized by pH-dependent swelling and sustained drug release profiles. Similar results were obtained, when Eudragit® E 100 was coprecipitated with Eudragit® L 100 from aqueous solutions [7].

The combination of Eudragit® E and Eudragit® L has not been investigated for the film coating of dosage forms. However, layering of the two polymers onto each other was studied by different researchers. A colon-targeted delivery system was developed when prior to coating with Eudragit® L 100, tablets were first subcoated with Eudragit® E 100 and hydroxypropyl methylcellulose [8]. In contrast, a Eudragit® E overcoat was employed to layer an initial dose onto Eudragit® L containing films [9].

Both Eudragit® E PO and Eudragit® L 100-55 have been used separately in dry coating processes of tablets. Dry powder coating, a water and organic solvent free

process, was developed to circumvent limitations of liquid based coating techniques for pharmaceutical dosage forms. The process has been successfully employed for various acrylic polymers [10-12]. Layering of Eudragit® E PO onto tablet cores was feasible without employing additional coating excipients [10]. In contrast, Eudragit® L 100-55 required pre-plasticization with triethyl citrate and the use of polyethylene glycol 3350 as primer to facilitate coating powder adhesion [12]. The drug release rate was increased when Eudragit® E PO coatings contained hydrophilic polymers [10].

The aim of the present study was to investigate the influence of Eudragit® E PO in Eudragit® L 100-55 film coatings applied by a dry powder coating technique on the drug release mechanism of theophylline from coated tablets. Dry powder coating was used for a polymer mixture which showed incompatibilities in solution [13]. The miscibility of Eudragit® L 100-55 was studied and Eudragit® E PO and the physiochemical properties of Eudragit® L 100-55/Eudragit® E PO blends were investigated.

7.2 MATERIALS

Eudragit® L 100-55 and Eudragit® E PO were donated by Evonik Industries AG (Piscataway, NJ). Triethyl citrate (TEC) was supplied by Vertellus Materials Inc. (Greensboro, NC). Talc USP (Imperial 500) was donated by Luzenac America, Inc. (Centennial, CO). Polyethylene glycol (PEG) 3350 NF was obtained from the DOW Chemical Company (Midland, MI). Lactose, monohydrate, NF, magnesium stearate, and the model drug theophylline (anhydrous) were purchased from Spectrum Chemical Mfg.

Corp. (Gardena, CA). Microcrystalline cellulose (Avicel® PH-101) was supplied by FMC Corp. (Newark, DE). Kollidon® K 30 was donated by BASF Corp. (Mount Olive, NJ) and Cab-O-Sil M-5P was supplied by Cabot Corp. (Tuscola, IL).

7.3 METHODS

7.3.1 Preparation of coating powders

Eudragit® L 100-55 was pre-plasticized employing a method that was first reported by Zheng et al. [11] for Eudragit® RS and Eudragit® RL PO and later adapted for the pre-plasticization of Eudragit® L 100-55 [12]. Eudragit® L 100-55 was pre-mixed with 30% TEC, based on the polymer weight using a high shear mixer. The powder blend was subsequently extruded employing a single screw extruder using a cylindrical die with an inner diameter of 6 mm (Randcastle Model RC 0750, Cedar Grove, NJ). The processing temperatures were set to 80ºC (zone 1), 110ºC (zone 2), 115ºC (zone 3), and 120ºC (die). The extrudate was cut into pellets using a Randcastle RCP-2.0 pelletizer and ground employing a cryogenic process (CF Mikro-Bantam Cryogenic Grinder, Micron Powder Systems, Summit, NJ). The pre-plasticized polymer powder was sieved for 15 minutes and particle size fraction between 100 and 200 mesh (75 - 150μm) was used for the dry powder coating experiments. The same process was used when Eudragit® L 100-55 was extruded in combination with Eudragit® E PO. Eudragit® L 100-55 was pre-blended with 30% TEC based on the weight of the enteric polymer using a mortar and

pestle before Eudragit® EPO was added. Different ratios of Eudragit® E PO and Eudragit® L 100-55 that contained 30% TEC were investigated including 3:7, 1:1, and 7:3. The temperature zones of the extruder were set to: zone 1 65ºC, zone 2 110ºC, zone 3 115ºC, and die 120ºC. The Eudragit® E PO/L 100-55 extrudate was processed identically as the pre-plasticized Eudragit® L 100-55 to obtain a fine powder.

7.3.2 Preparation of core tablets

Theophylline anhydrous (15%), Avicel® PH 101 (66.25%), lactose monohydrate (15%), and Kollidon® K 30 (3%) were mixed in a low shear blender for 15 minutes. Subsequent to the addition of the magnesium stearate (0.5%) and colloidal silicon dioxide (0.25%), the mixture was blended for 5 more minutes. The tablets were compressed using a single stage press (F-press, Stokes, Bristol, PA) employing deep concave 5 mm punches. The tablet weight was 79.2±1.2 mg (n = 6, standard deviation). The tablet hardness (9.1±0.6 kg, n = 6, standard deviation) was determined using a tablet tester (WTP-3, Heberlein &. Co. AG, Wattwil, Switzerland).

7.3.3 Powder coating of tablets

Theophylline tablets were powder-coated in a modified laboratory scale spheronizer (Model 120, G.B. Caleva, Dorset, UK) as first reported by Cerea et al. and Zheng et al. [10, 11]. The anti-tack agent talc and the low-melting coating excipient PEG 3350 were each added in a 10% ratio to the processed polymer, based on the weight of

the Eudragit® E PO/pre-plasticized Eudragit® L 100-55 mixture. PEG 3350 was also used as primer with a 2% weight gain, based on the tablet weight, to promote coating powder adhesion as previously recommended [12]. The batch size was 40 g of tablets. The coating conditions for the different Eudragit® E PO/pre-plasticized Eudragit® L 100-55 ratios are presented in Table 7.1. The temperature of the coating bed was monitored employing a Fluke 61 Infrared Thermometer (Fluke Corporation, Everett, WA). The feeding rate of the coating powder onto the tablets cores was adjusted according to the capacity of the coating powder to adhere. Subsequent to the application of the primer, the coating powder was manually applied at a rate of about 3 g/min until a polymer weight gain of approximately 10% was obtained and then reduced to 0.5 g/min. Following coating powder layering, the tablets were thermally treated in the operating spheronizer at 60ºC for 6 hours.

7.3.4 Particle size distribution

The particle size distribution of Eudragit® E PO was analyzed using laser light diffraction (Malvern Mastersizer S, Malvern Instrument Limited, Malvern, Worcestershire, UK). D_v 10, D_v 50, and D_v 90, the cumulative percent undersize, were determined using the approximate diffractive index of Eudragit® E PO (n_D^{20} = 1.3899) in purified water (n_D^{20} = 1.3300).

7.3.5 Modulated differential scanning calorimetry

Modulated differential scanning calorimetry (MDSC) was performed using a Thermal Advantage Model 2920 (TA Instruments, New Castle, DE) to characterize the thermal properties of Eudragit® E PO, pre-plasticized Eudragit® L 100-55, their physical mixtures, their melt extrudates, and free films of their mixtures. Universal Analysis 2000 software was employed to determine the inflection glass transition temperature using the reverse heat flow of the second heating cycle. Prior to analysis, the samples were sealed in aluminum pans (Kit 0219-0041, Perkin-Elmer Instruments, Norwalk, CT). The temperature ramp rate was 3°C/min at a modulation rate of ±1.00°C every 60 seconds. Ultrahigh pure nitrogen was employed as purge gas at a flow rate of 150 ml/min.

7.3.6 Drug release study

In vitro dissolution testing was conducted to investigate the release rate of theophylline from powder-coated tablets in either 900 mL of 0.1N HCl or in 900 mL pH 6.8, 50 mM phosphate buffer for 12 hours. Furthermore, the USP Drug Release Standard for Enteric Coated Articles Method A was used to characterize the enteric release properties of the coated tablets. Following two hours dissolution in 750 mL, 0.1N HCl, 250 mL of 0.2M tribasic sodium phosphate solution were transferred to the dissolution vessel to adjust the pH of the dissolution medium to 6.8 ± 0.05. The drug release study was then resumed for 2 more hours. All dissolution media were maintained at 37 °C and agitated at 50 rpm using USP 30 Apparatus 2 (Vankel VK 7000; Vankel Industries Inc.,

Cary, NC). The dissolution properties of the coated tablets were investigated by placing three tablets into each of three dissolution vessels respectively (n = 3 x 3 tablets/vessel). Samples were withdrawn by an autosampler (Vankel VK 8000; Vankel Industries Inc., Cary, NC).

UV Analysis was performed to analyze the dissolution samples for theophylline content using a μQuant (Bio-Tek® Instruments Inc., Winooski, Vermont) at the detection wavelength 278 nm. Prior to analysis, the samples were filtered using 0.45 μm nylon filters and diluted with an equal volume of dissolution medium. Linearity was demonstrated from 1 to 25 μg/mL ($R^2 > 0.999$). One-way ANOVA followed by Tukey's HSD post-hoc test was conducted using SPSS Version 15.0.

7.3.7 Film preparation and dissolution

Free films were prepared from mixtures of Eudragit® E PO and pre-plasticized Eudragit® L 100-55 that contained 30% TEC based on the polymer weight. The polymer mixture was blended with 10% PEG 3350 using a mortar and pestle. Following compression into films using a compression force of 10 kN on 22 cm^2 of film for 3 minutes to ensure a dense powder packing (Carver Laboratory Press, Model M, ISI Inc., Round Rock, TX), the samples were cured in a static oven at 60ºC for 24 hours. The compression force was reduced during the thermal treatment to 10 N.

Film samples of 3x3 mm were immersed in 15 mL of 0.1N HCl and shaken at 100 rpm at 37ºC for 2 hours using a Lab-Line® Orbit Environ-Shaker (Lab-Line Inctruments Inc., Melrose Park, IL). Following the addition of 5 mL of 0.2M tribasic sodium

phosphate solution to adjust the pH of the dissolution medium to 6.8 ± 0.05, the film dissolution was continued for 2 more hours.

7.3.8 Scanning electron microscopy

The surface morphology of powder-cast films prior to and after dissolution and coated tablets was analyzed using a LEO 1530 Gemini scanning electron microscope (Zeiss/LEO, Oberkochen, Germany) operated at 10 kV. The samples were sputter coated with platinum/palladium (80:20) using a Cressington Sputter Coater 208 HR equipped with a Thickness Controller MTM 20 (Cressington Scientific Instruments Ltd., Watford, UK) at 20 mA to a coating thickness of 15 nm.

7.3.9 Fourier transform infrared spectroscopy

To characterize interactions occurring between Eudragit® E PO and pre-plasticized Eudragit® L 100-55 Fourier transform infrared spectroscopy was conducted using a Nicolet Magna IR-560 FT-IR spectrometer. Eudragit® E PO, Eudragit® L 100-55, pre-plasticized Eudragit® L 100-55, their physical mixtures and their heat-treated physical mixtures were compressed with potassium bromide into pellets under vacuum using a compression pressure of 10 tons to acquire the transmittance spectra of the materials.

7.4 RESULTS AND DISCUSSION

7.4.1 Powder coating of theophylline tablets

The Hoftyzer/van Krevelen 3-D solubility parameters solubility parameter of Eudragit® E PO and Eudragit® L 100-55 were determined to be 21.8 $(J/cm^3)^{0.5}$ and 23.1 $(J/cm^3)^{0.5}$ respectively at 25ºC. It has been reported that differences in drug/excipient solubility parameters of <7 $MPa^{0.5}$ were used to predict significant miscibility between the components [14]. Due to the restricted mobility of polymer segments, the Flory-Huggins theory has been widely used for the mixing of polymers [15, 16]. The interaction parameter χ_{12} can be calculated using the following equation:

$$\chi_{12} = (V_r / RT)(\delta_1 - \delta_2)^2 \quad (1)$$

where V_r is the reference volume (100 cm^3/mol for polymers [16]), R is the universal gas constant, T is the absolute temperature, δ are the solubility parameter, and indices 1 and 2 refer to the blended polymers. If the interaction parameter χ_{12} is smaller than the critical value of the interaction parameter, the polymer blend was considered miscible [16]. The critical value of the interaction parameter $(\chi_{12})_{cr}$ can be calculated from the degree of polymerization (N):

$$(\chi_{12})_{cr} = 0.5 (N_1^{-0.5} + N_2^{-0.5}) \quad (2)$$

According to the calculated interaction parameter 0.1 at 25ºC and the critical interaction parameter 0.0, Eudragit® E PO and Eudragit® L 100-55 were expected to be immiscible.

Theophylline tablets were powder coated with Eudragit® E PO/Eudragit® L 100-55 powder mixtures in a modified spheronizer as used for the single polymers [10, 12].

Previously, Eudragit® E PO was coated onto theophylline tablets at a bed temperature of 55-60ºC, whereas pre-plasticized Eudragit® L 100-55 containing 30% TEC based on the polymer weight was layered onto tablets using a bed temperature of 70-75ºC. A priming layer of PEG 3350 was required for the powder coating of tablets with pre-plasticized Eudragit® L 100-55 as well as the addition of PEG 3350 in a 10% ratio to the coating powder [12]. Talc has been commonly used in a 10% ratio in powder coating applications [11]. Depending on the polymer ratio of the physical mixtures, the coating conditions were adjusted as presented in Table 7.1. Increasing Eudragit® E PO amounts required lower coating temperatures. However, the curing conditions were unchanged for all investigated formulations. The coating powders prepared from the physical polymer mixtures adhered well onto the tablet cores.

Depending on the polymer ratio, powder coating with hot-melt extruded mixtures of Eudragit® E PO and Eudragit® L 100-55 containing 30% TEC based on the weight of the enteric polymer resulted in no or uneven coating powder adhesion. Different formulation factors and processing parameters were varied to improve adhesion of the hot-melt extruded powders, including reduction of talc concentration in the coating formulation as suggested by Kablitz et al. [17], the increase of the TEC and PEG 3350 levels in the coating powder, the elimination of PEG 3350 as primer, and the variation of the coating bed temperature from 55ºC to 90ºC. However, sticking of the extruded coating powder formulations to the tablet cores was not enhanced at the investigated processing conditions. There was no coating powder adhesion observed for the hot-melt extruded 3:7 ratio whereas formulation of the 1:1 and 7:3 ratio resulted in uneven coating powder layering onto the tablet cores. Free film studies revealed, that there was no film

formation occurring for a powder-cast film containing an extruded 3:7 mixture of Eudragit® E PO and Eudragit® L 100-55 that was plasticized with 30% TEC based on the weight of the enteric polymer when cured at 60ºC for 24 hours (data not shown). In contrast, film formation was observed for the 1:1 and 7:3 ratios.

DSC analysis was performed to investigate the distribution of the plasticizer within the extruded polymer mixtures. As shown in Figure 7.1, Eudragit® E PO and Eudragit® L 100-55 were not miscible at the employed ratios and extrusion conditions. The thermograms were characterized by two glass transition temperatures. Eudragit® E PO did not plasticize the enteric polymer. In contrast, thermal analysis of coprecipitates of Eudragit® E PO and Eudragit® L 100-55 demonstrated miscibility [6, 18]. However, Gallardo et al. proposed that Eudragit® L 100-55 was plasticized by Eudragit® E PO, whereas Moustafine et al. detected glass transition temperatures at significantly higher temperatures than calculated values using the Gordon-Taylor equation. Hot-melt extruded mixtures of Eudragit® E PO and Eudragit® L 100-55 that were plasticized with TEC were characterized by an uneven distribution of the plasticizer and a higher affinity of TEC for Eudragit® E PO (Figure 7.1 B). At the 1:1 and 7:3 ratio the glass transition corresponding to Eudragit® L 100-55 was approximately the same as of pure bulk polymer (123.7 ± 0.6°C, [12]). Non-miscibility of the polymers and uneven distribution of the plasticizer resulted in a large difference of the two glass transition temperatures and thus in insufficient coating powder adhesion of the hot-melt extruded mixtures.

The DSC thermograms of the physical mixtures also showed some redistribution of the plasticizer (Figure 7.1 A), however, not as strong as for the hot-melt extruded mixtures. Eudragit® L 100-55 containing 30% TEC based on the polymer weight was

characterized with a glass transition at 65.29ºC, whereas Eudragit® E PO showed a transition at 43.20ºC. The glass transitions of Eudragit® E PO occurred at lower temperatures and the glass transitions of Eudragit® L 100-55 were increased in the physical mixtures. Uneven plasticizer distribution in film coatings prepared from aqueous dispersions of different polymers has been reported in the literature. Lecomte et al. reported a higher affinity of dibutyl sebacate to ethylcellulose than to Eudragit® L 30 D-55 [19]. Different affinity of the plasticizer to the film forming polymers may result in redistribution within the polymer mixture and may affect the physical stability upon storage. Adequate curing and sufficient pre-plasticization time prior to coating to ensure "equilibrated" plasticizer uptake by the polymers were shown to prevent changes of the drug release profiles during storage [19]. Generally, a homogeneous plasticizer distribution throughout the polymer is recommended [20].

DSC profiles of powder cast films from Eudragit® E PO/Eudragit® L 100-55 physical mixtures that also contained 10% PEG 3350 as low melting coating excipient are presented in Figure 7.1 C. The addition of PEG 3350 was shown to be essential for film formation of powder-coated Eudragit® L 100-55 films [12]. Due to curing at 60ºC for 24 hours and the PEG 3350 content, different thermograms were expected compared to the physical mixtures. The glass transitions of Eudragit® E PO occurred at lower temperatures due to repartitioning of TEC. Due to the plasticizing effect of PEG 3350 on the enteric polymer, the glass transitions of Eudragit® L 100-55 were also reduced for the 3:7 and 1:1 ratio. For the 7:3 ratio the TEC redistribution effect was more pronounced than the plasticizing effect of PEG 3350, and thus the glass transition of Eudragit® L 100-55 was increased to 106.79ºC. The thermogram of Eudragit® L 100-55 containing 30%

TEC and 10% PEG 3350 was characterized by one glass transition and the disappearance of the PEG 3350 melting peak due to complete miscibility [12]. The thermograms of powder-cast films from the 1:1 and 3:7 ratio both showed an endothermic transition due to melting of the PEG 3350 between 52 and 54ºC. The melting point was decreased compared to the one of bulk PEG 3350, which occurred at approximately 61ºC [12] and was characterized by a low heat of fusion. Increasing Eudragit® E PO concentrations in the powder-cast films hence resulted in a decreasing miscibility of PEG 3350 in the polymer mixture.

7.4.2 Theophylline release study

The drug release profiles of theophylline tablets that were powder coated are presented in Figure 7.2. The core tablets disintegrated quickly and theophylline was completely released after 30 minutes of dissolution in both 0.1N HCl and pH 6.8 phosphate buffer. The drug release from the powder-coated tablets was strongly dependent on the pH of the dissolution medium. As expected, in 0.1 N HCl the drug release rate increased with increasing Eudragit® E PO concentration in the film coating. Since Eudragit® L 100-55 is soluble above pH 5.5, increasing fractions of the enteric polymer in the film coating resulted in an accelerated release in pH 6.8 phosphate buffer. Not only the ratio of the polymers but also the polymer weight gain affected the drug release rate. The variability of the dissolution profiles decreased with higher polymer weight gains. Since thicker film coatings result in longer diffusion pathways for dissolution medium to penetrate into the core, for drug molecules to exit the core, and for

dissolved polymer molecules to leave of the film, higher polymer weight gains resulted in a decrease in drug release rate. The effect of weight gain was most pronounced for films with high concentration of Eudragit® E PO in pH 6.8 buffer. During film dissolution in pH 6.8 buffer, strong swelling was observed for the powder-cast films and approximately doubled its size, whereas the films did not swell in acid. Water imbibition in the Eudragit® E PO matrix may weaken the mechanical strength of the film coating and result in a fast release at low coating levels. The energy at break of Eudragit® L 30 D-55 films was shown to increase after immersion in 0.1N HCl [21].

SEM micrographs in Figure 7.3 of the surface of theophylline tablets that were powder-coated with physical mixtures of Eudragit® E PO and pre-plasticized Eudragit® L 100-55 show a dense film. As in previous powder-coating studies, the film surface of powder coated films is not as even as the one of film coatings that were prepared using aqueous or organic coating processes and is characterized by some individually visible, non-fused polymer particles [10, 12, 22].

Figure 7.4 shows the dissolution profiles of powder-coated theophylline tablets in pH 6.8 phosphate buffer following dissolution in 0.1N HCl for two hours. The 7:3 ratio was not tested, since more than 90% of theophylline were release after 2 hours in 0.1N HCl. After the pH change of the dissolution medium, the drug release rate increased for both investigated formulations. To further investigate the drug release mechanism, SEM studies were performed. The powder-cast film of Eudragit® E PO and pre-plasticized Eudragit® L 100-55 in a 7:3 ratio was initially characterized by a dense and smooth surface (Figure 7.5 A). After dissolution in 0.1N HCl for 1 hour, pore formation was observed that did not change noticeably after immersion for an additional hour in acidic

medium (Figure 7.5 B and C). Following two hours in 0.1N HCl, the pH of the dissolution medium was increased to pH 6.8. Change of the pH of the medium resulted in dissolution of the remaining Eudragit® L 100-55, noticeable swelling of the film and loss of integrity.

As presented in Figure 7.5 B and C, large polymer domains were dissolved out of the film, leaving large cavities in the film coating. The influence of the preparation technique for films made from polymer blends was previously shown to significantly affect the microstructure of polymer films and thus drug release profiles [23]. Due to the different film forming mechanism, polymer films prepared from organic solution are characterized by a high degree of polymer-polymer interpenetration while separate polymer domains were present in films based on aqueous dispersions. This phenomenon affected the swelling behavior of polymer films that were composed of ethylcellulose and Eudragit L and thus the drug release kinetics of coated propranolol HCl pellets. Swelling of Eudragit® L was decreased in films prepared from organic solution due to a high degree of polymer interpenetration [23]. The particle size distribution of Eudragit® L 100-55 that was pre-plasticized with 30% TEC was previously analyzed using laser light diffraction [12]. The D_v10, D_v50, and D_v90 values were 35.13 μm, 77.50 μm, and 147.58 μm, respectively. The span index was 1.451. In contrast, bulk Eudragit® E PO was characterized by a much smaller particle size using the same analytical technique. The D_v10, D_v50, and D_v90 values were determined to be 0.69 μm, 7.13 μm, and 15.93 μm, respectively. The span index was 1.451. The mean particle size of Eudragit® L 30 D-55, Eudragit® RS 30 D, and Eudragit® NE 30 D latexes was shown to be between 100 and 200 nm [24]. The coating powder particle size used for the dry coating of theophylline

tablets was higher, thus the degree of polymer interpenetration of blended polymers is expected to be lower in dry coating applications compared to aqueous and organic coating processes. As a result larger polymer domains are dissolved out of the film coating during dissolution.

7.4.3 FT-IR results

The characteristic bands of the FT-IR transmittance spectrum of Eudragit® E PO were at 2770 cm^{-1} and 2820 cm^{-1} for the absorption of the dimethyl amino group [20]. The spectrum of Eudragit® L 100-55 was characterized by one band at 1705 cm^{-1} that is assigned to the C=O vibration of the carboxylic acid group [20]. Both spectra showed a band at 1730 cm^{-1} corresponding to the C=O vibration of the esterified carboxyl group [20]. In FT-IR spectra of copolymer complexes, the characteristic bands of the carboxylic acid and the ternary amino group were reduced in intensity or disappeared, whereas new bands appeared at 1560 cm^{-1} and at 2560 cm^{-1} [6, 18]. The new bands were assigned to the formation of carboxylate groups and ionized dimethylamino groups and were not observed in the current study. As shown in Figure 7.6, no new band or band shifts were detected when the FTIR spectra of the single components, physical mixture, and the annealed physical mixture of different ratios were compared. Although the intensity of the bands decreased for the annealed physical mixture, the relative band intensity was unchanged. Upon heating, the plasticizer redistributed within the polymer mixture. The incorporation of plasticizers into a polymer was shown influence the density of the polymer [25] and thus may affect the transmittance. TEC could not be detected due to

structural similarity such as ethyl ester. The only difference in relative band intensity of physical mixture and annealed physical mixture was observed for bands at 1470cm^{-1} and 1460cm^{-1} which can be assigned to CH_2 and CH_3 bending corresponding to a minor variation in ratio of the copolymers. Consequently binding interactions and complex formation between Eudragit® E PO and Eudragit® L 100-55 were not expected during film formation from the physical mixtures. The bands at 2370cm^{-1} and 2350cm^{-1} were attributed to atmospheric carbon dioxide.

7.4.4 Physical stability of powder coated tablets

The physical stability of theophylline tablets that were powder-coated with a 25% weight gain of Eudragit® E PO and pre-plasticized Eudragit® L 100-55 in a 1:1 ratio was investigated using dissolution testing. The application of a talc overcoat was not necessary since the film coating did not show tackiness. The powder-coated tablets were sealed in HDPE containers with desiccant to exclude the influence of humidity during storage at 25ºC/60% RH or 40ºC/75% RH for 4 weeks. Prior to dissolution testing, the samples were equilibrated to ambient temperatures for 24 hours. The theophylline release profiles as function of storage time and conditions are presented in Figure 7.7. One-way ANOVA was employed to determine statistical differences of the cumulative theophylline release percentage from powder-coated tablets stored either at 25ºC/60% RH or at 40ºC/75% RH for 4 weeks at different time points. The ANOVA p values are listed in Table 7.2. Only the first time point demonstrated a statistical difference in the data both for dissolution in 0.1N HCl and pH 6.8 phosphate buffer. At the remaining time

points there was no statistical difference in the cumulative drug release percentage data ($p<0.05$). Tukey's HSD revealed a statistical difference of the initial cumulative drug release at 1 hour compared to 4 weeks of storage at either 25ºC/60% RH or 40ºC/75% RH ($p<0.05$). However, there was no significant difference between the cumulative theophylline release between the samples stored at 25ºC/60% RH or 40ºC/75%. The drug release profiles were shown to be identical, besides the first time point which was taken after one hour of dissolution. Storage with desiccant can affect the hydration state of the polymer film and thus influence the drug release rate. The cumulative theophylline release at 1 hour was slightly more reduced in pH 6.8 medium than in 0.1N HCl. In buffered medium Eudragit® L 100-55 dissolved out of the film coating, whereas Eudragit® E PO was the film forming matrix. Plasticizer migration from the enteric polymer phase to Eudragit® E PO phase stabilized the film matrix. However, there was only little impact on the release profile.

7.5 CONCLUSION

Powder coating technology was successfully employed for polymer blends that demonstrated incompatibilities in solution. Coating with Eudragit® E PO/Eudragit® L 100-55 mixtures provided dosage forms with pH-dependent release profiles. The results of MDSC and SEM demonstrated non-miscibility of Eudragit® E PO and Eudragit® L 100-55 in different ratios and for diverse processing methods. The calculated Flory-Huggins interaction parameter based on solubility parameters supported the data. Due to

the film formation process and particle size of the copolymers the degree of polymer interpenetration of the blended polymers powders was less than expected in liquid based coating processes. The theophylline release rate from coated tablets was significantly controlled by the ratio of Eudragit® E PO and Eudragit® L 100-55 and the coating level. Different affinity of the plasticizer to the film forming polymers resulted in redistribution of the plasticizer during the curing phase of the coating process and slightly affected the storage stability of the powder-coated tablets.

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7.7 TABLES AND FIGURES

Table 7.1: Processing parameters and formulations for the powder-coating of theophylline tablets.

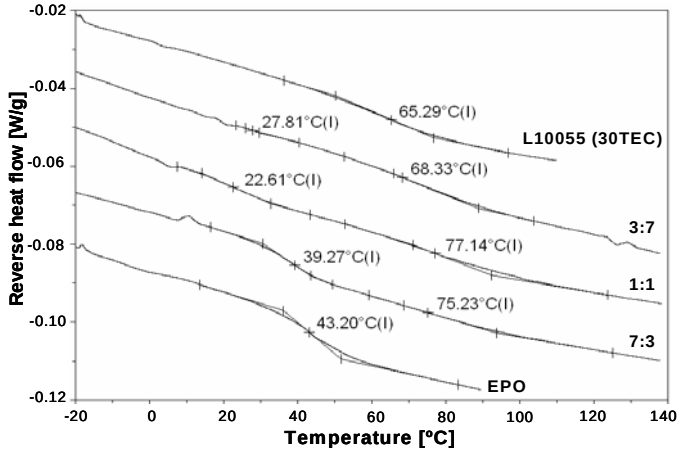
	Formulation I	**Formulation II**	**Formulation III**
Eudragit® EPO	30%	50%	70%
Eudragit® L 100-55 (pre-plasticized with 30% TEC based on the polymer weight)	70%	50%	30%
PEG 3350	10% w/w based on polymer powder weight		
Talc	10% w/w based on polymer powder weight		
Primer	2% PEG 3350*		
Rotation speed	170 rpm		
Coating bed temperature	70-75ºC	70-75ºC	65-70ºC
Curing rotation speed	120 rpm		
Curing bed temperature	60ºC		

*weight gain, based on tablet weight

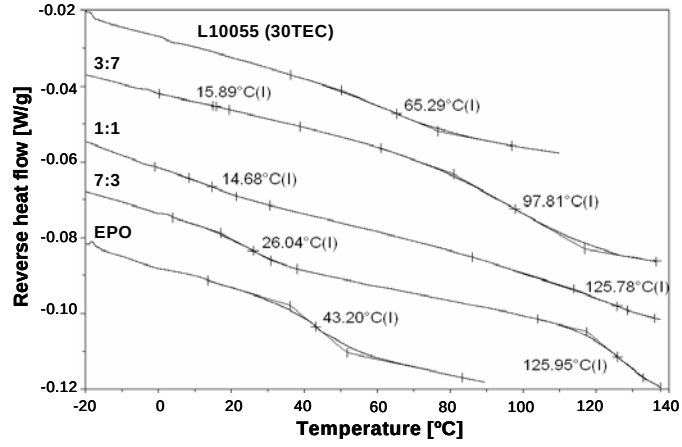
Table 7.2: p values from One-way ANOVA for percent theophylline released from powder-coated tablets initially and after one month of storage.

Dissolution time	1h	2h	3h	4h	5h	6h
p value for drug release in 0.1N HCl	0.001	0.199	0.334	0.057	0.931	0.863
p value for drug release in pH 6.8 buffer	0.006	0.053	0.142	0.255	0.613	0.887

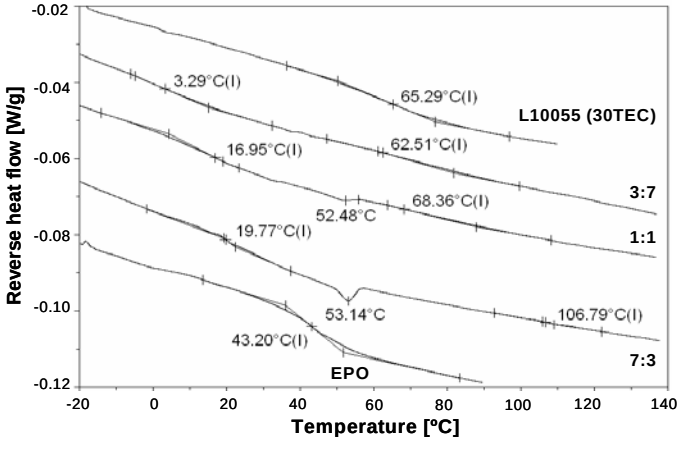
Figure 7.1: MDSC thermograms of different ratio Eudragit® E PO / pre-plasticized Eudragit® L 100-55 mixtures. A: Physical mixture. B: Hot-melt extruded mixture. C: Powder-cast film that additionally contained 10% PEG 3350 based on the polymer weight.



(A)

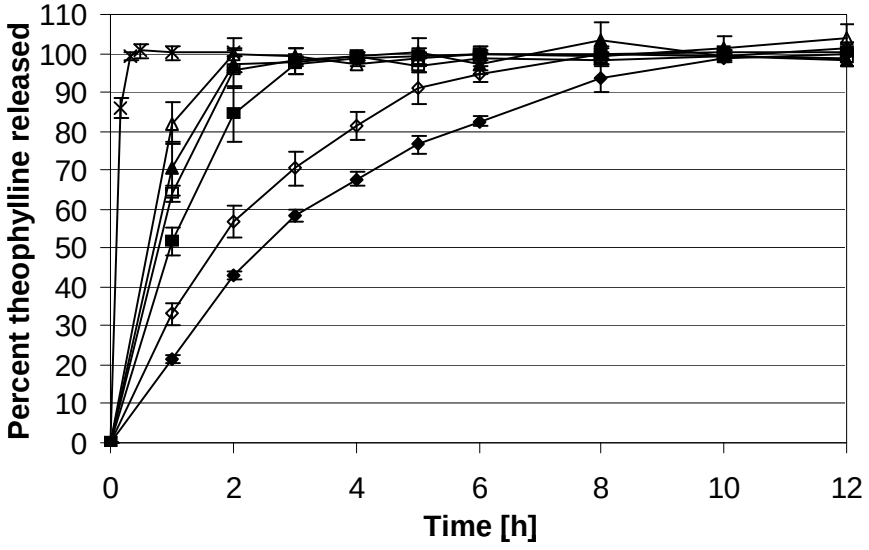


(B)

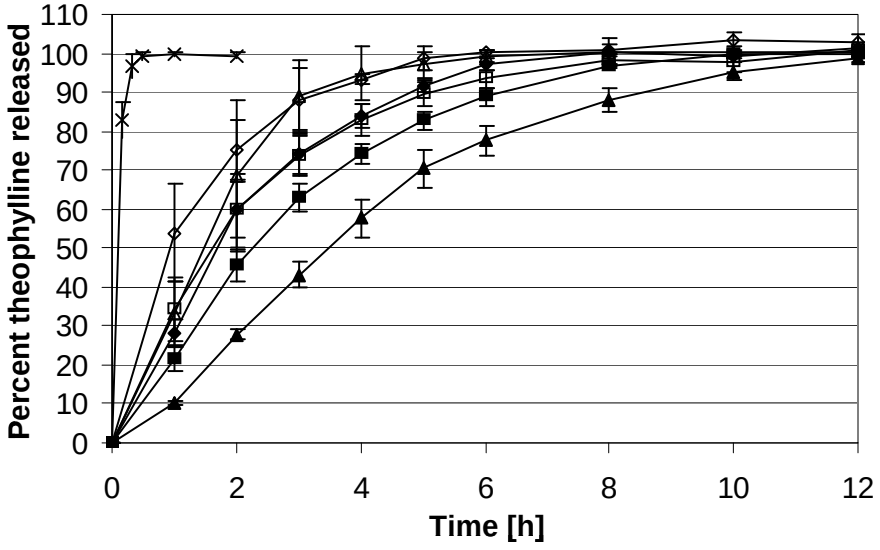


(C)

Figure 7.2: Influence of Eudragit® E PO / pre-plasticized Eudragit® L 100-55 ratio and coating level on the release of theophylline from powder-coated tablets using USP 30 apparatus 2. (A) Dissolution in 900mL of 0.1N HCl. (B) Dissolution in 900mL pH 6.8 50mM phosphate buffer. ◊: 3:7, 15% weight gain. ♦: 3:7, 25% weight gain. □: 1:1, 15% weight gain. ■: 1:1, 25% weight gain. Δ: 7:3, 15% weight gain. ▲ 7:3, 25% weight gain. x: core tablet. (Standard deviation, *n* = 3 x 3 tablets/vessel.)



(A)



(B)

Figure 7.3: Influence of Eudragit® E PO / pre-plasticized Eudragit® L 100-55 ratio on surface morphology of SEM micrographs of powder-coated tablets. A: 3:7. B: 1:1. C: 7:3.

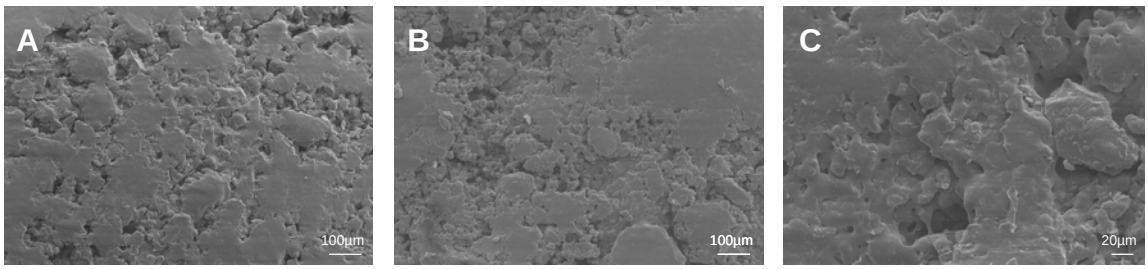


Figure 7.4: Influence of Eudragit® E PO / pre-plasticized Eudragit® L 100-55 ratio on the release of theophylline from powder-coated tablets using USP 30 apparatus 2. Dissolution in 750mL of 0.1N HCl for 2 hours followed by 2 hours in 1000mL pH 6.8 50mM phosphate buffer after pH adjustment at 37ºC and 50 rpm. Total weight gain: 25%. ■: 1:1. ▲: 3:7. (Standard deviation, *n* = 3 x 3 tablets/vessel.)

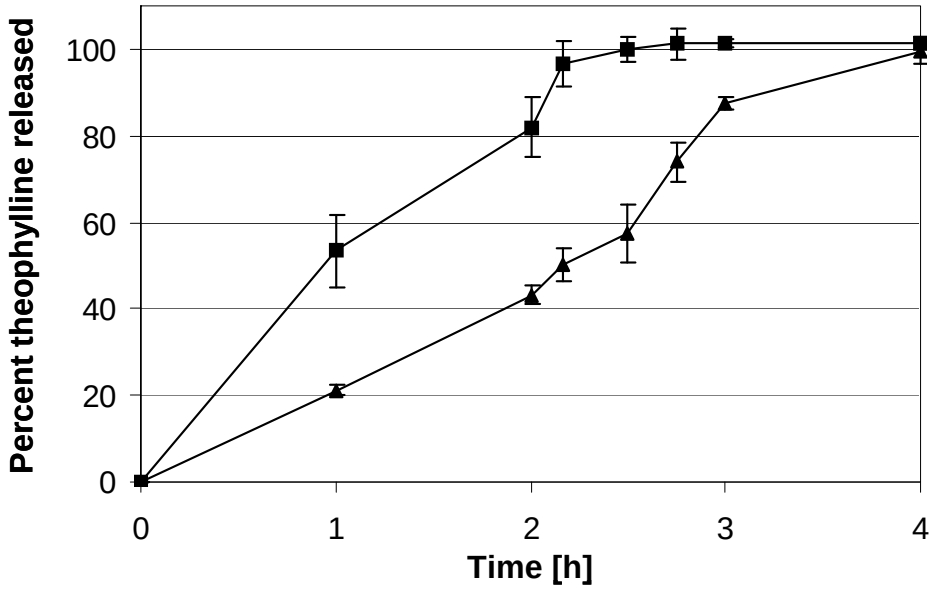


Figure 7.5: SEM micrographs of surface of Eudragit® E PO / pre-plasticized Eudragit® L 100-55 (ratio: 3:7) powder-cast film. Dissolution 0.1N HCl for 2 hours followed by 2 hours pH 6.8 50mM phosphate buffer after pH adjustment at 37ºC. A: Initial. B: after 1 hour in 0.1N HCl. C: after 2 hours in 0.1N HCl. D: after 2 hours in 0.1N HCl followed by 2 hours in pH 6.8 buffer.

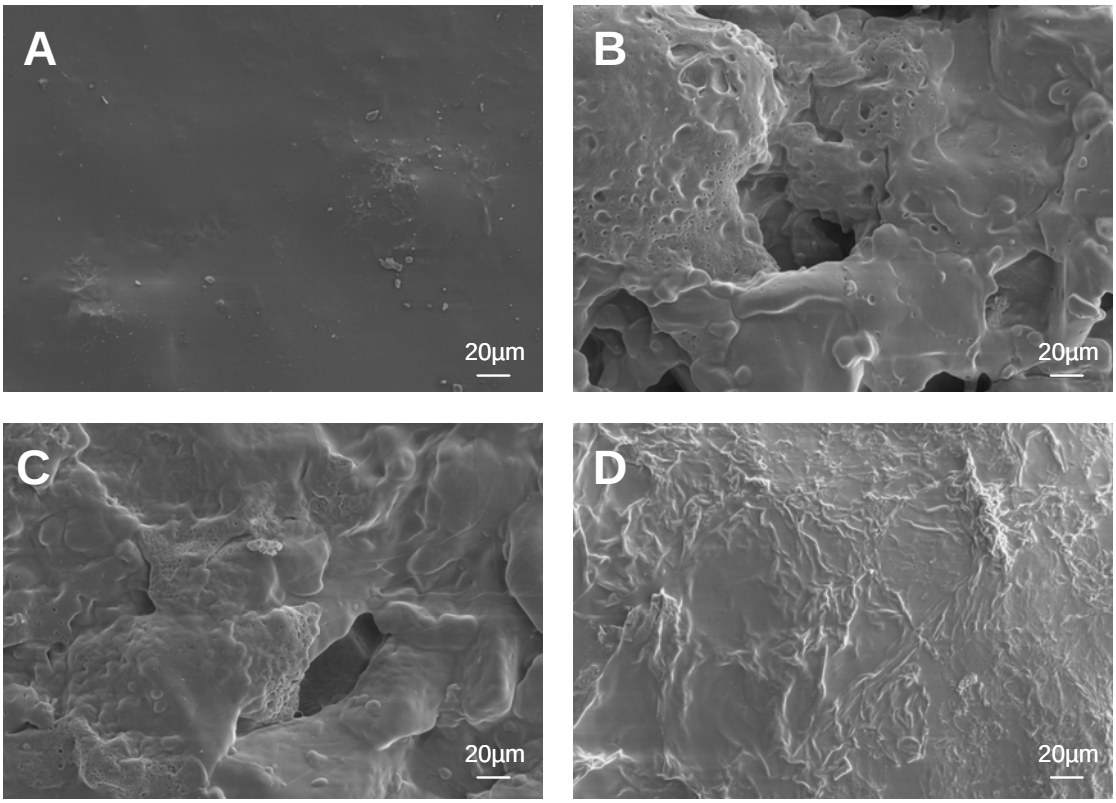
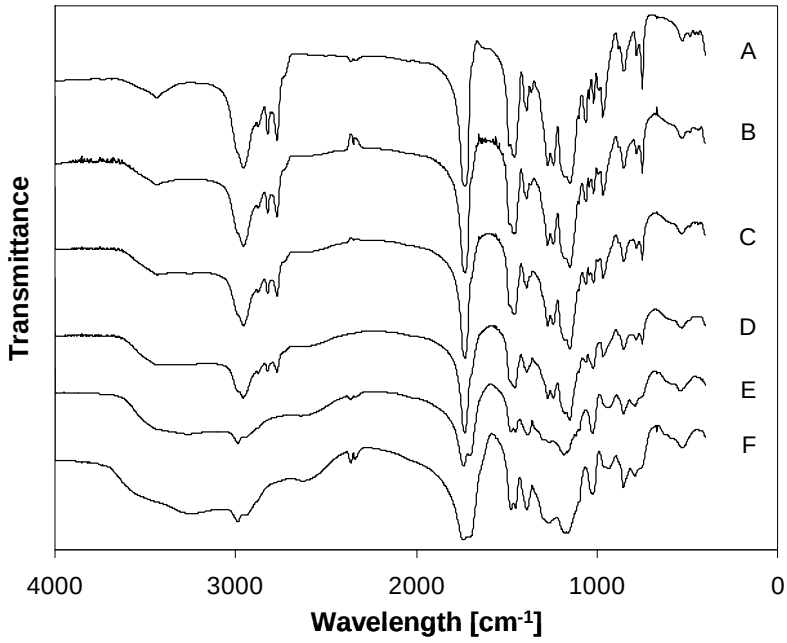
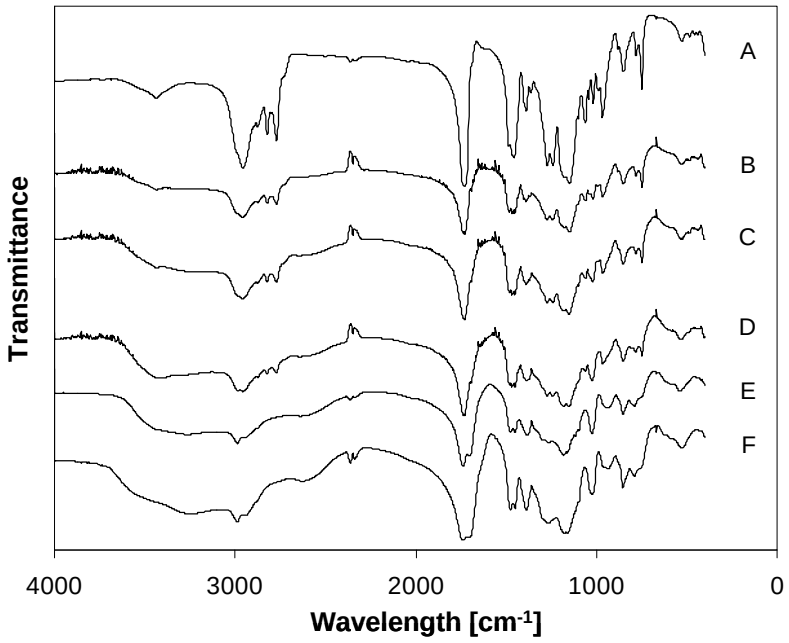


Figure 7.6: FT-IR spectra of Eudragit® L 100-55, pre-plasticized Eudragit® L 100-55, Eudragit® E PO, and pre-plasticized Eudragit® L 100-55/Eudragit® E PO mixtures. I: physical mixtures. II: physical mixtures heated at 80ºC for 3 hours and 60ºC for 24 hours. A: Eudragit® EPO. B: 7:3. C: 1:1. D: 3:7. E: pre-plasticized Eudragit® L 100-55 (30% TEC). F: Eudragit® L 100-55.

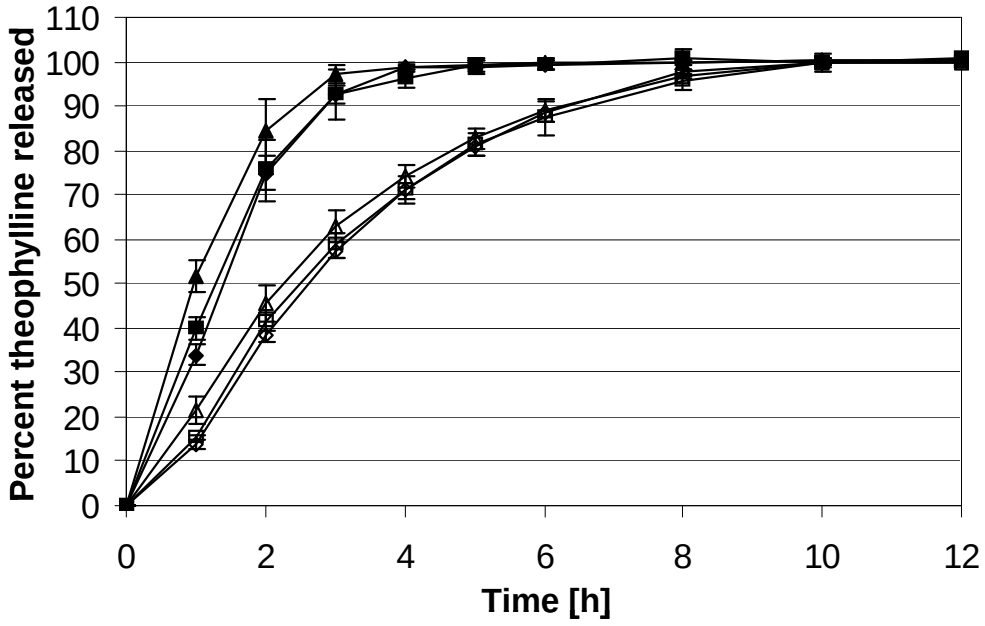


(I)



(II)

Figure 7.7: 4 week stability of theophylline tablets powder-coated with Eudragit® E PO / pre-plasticized Eudragit® L 100-55 in a 1:1 ratio using USP 30 apparatus 2 at 37ºC and 50 rpm. Dissolution in 900mL of dissolution medium. Total weight gain: 25%. ▲: initial dissolution in 0.1N HCl. Δ: initial dissolution in pH 6.8 50mM phosphate buffer. ♦: 4 weeks at 25ºC / 60% RH, 0.1N HCl. ◊: 4 weeks at 25ºC / 60% RH, pH 6.8 50mM phosphate buffer. ■: 4 weeks at 40ºC / 75% RH, 0.1N HCl. □: 4 weeks at 40ºC / 75% RH, pH 6.8 50mM phosphate buffer. (Standard deviation, *n* = 3 x 3 tablets/vessel.)



Chapter 8: Summary and Conclusion

In this research project, I investigated the processing parameters and formulation factors influencing the dry-powder coating of tablets with pre-plasticized Eudragit® L 100-55. The model drugs chlorpheniramine maleate (CPM) and sodium valproate were previously shown to require large weight gains of enteric polymer to delay the drug release in acidic media using aqueous coating techniques.

Unlike aqueous coating, powder coating reduced partitioning of the drug into the film coating during the coating process. Polyethylene glycol 3350 (PEG 3350) was used as primer for powder coating of tablets with pre-plasticized Eudragit® L 100-55 and was also added to the coating formulation to enhance coating powder adhesion and film formation. Following powder layering, the powder-coated tablets were thermally cured to ensure complete film formation and drug release stability. The drug release properties of powder-coated tablets were dependent on the curing time, coating level and plasticizer content. The stability of the powder-coated CPM tablets was confirmed at 25ºC/60% RH over a storage time of 12 weeks.

Sodium valproate tablets were shown to require high weight gains of powder-coated Eudragit® L 100-55 to pass the USP enteric test. The application of a Eudragit® E PO or Eudragit® RL PO subcoat assisted with adhesion of the enteric polymer onto the tablet cores and reduced the amount of enteric polymer required for enteric protection. PEG 3350 and Methocel® K4M were added to the subcoat formulation to increase the drug release in buffered media. Effectiveness as pore forming agent was a function of

miscibility of the excipient with the polymers. Storage stability was confirmed for powder-coated sodium valproate tablets at 25ºC/60% RH for all investigated formulations. Storage at 40ºC/75% RH resulted in fluctuations in drug release over 12 weeks. Loss of plasticizer in the film coating at 40ºC affected the storage stability of the powder-coated sodium valproate tablets.

Factors influencing film formation were investigated including thermal stability of the components, melt viscosity, and surface free energy of the copolymer. Thermogravimetric analysis revealed stability of the components at the investigated curing conditions. Low melt viscosity and high surface free energy were previously shown to accelerate polymer particle fusion and surface leveling in dry coating processes. The plasticizer triethyl citrate (TEC) reduced the relative melt viscosity and increased the surface free energy of the polymer. The addition of PEG 3350 resulted in a decrease in melt viscosity, however did not affect the surface free energy of Eudragit® L 100-55. Mechanical testing of powder-cast films demonstrated an increase in both the elongation and puncture strength with increasing curing times as criterion for polymer particle fusion. Film formation was shown to progress faster at high plasticizer levels.

Powder coating with Eudragit® E PO/Eudragit® L 100-55 was used to manufacture dosage forms with pH-dependent release profiles. The Flory-Huggins interaction parameter based on solubility parameters as well as the results of differential scanning calorimetry, Fourier transform infrared spectroscopy and scanning electron microscopy demonstrated non-miscibility of Eudragit® E PO and Eudragit® L 100-55 in different ratios for diverse processing methods. The theophylline release rate from coated tablets was significantly controlled by the ratio of Eudragit® E PO and Eudragit® L 100-

55. Lower affinity of the plasticizer to the enteric polymer influenced the plasticizer distribution within the film coating.

In conclusion, dry powder coating, a completely liquid free process, was demonstrated to be an efficient method to coat tablets with Eudragit® L 100-55. The coating formulations and processing parameters were adjusted for each model drug. Coating additives were shown to influence parameters for film formation such as melt viscosity and surface free energy. The incorporation of Eudragit® E PO in Eudragit® L 100-55 film coatings provided dosage forms with a broad range of pH-dependent release profiles.

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Vita

Dorothea Sauer was born in Dresden, Germany on March 22, 1979, daughter of Drs. Helgard and Wolfgang G. Sauer. She graduated from high school (Pestalozzigymnasium, Dresden, Germany) in July 1997. In fall of the same year she joined the pharmacy program of the university Freie Universität Berlin, Germany. After completion of the lower-division classes, she took the first German licensure examination for pharmacists in summer 1999. The second German licensure examination for pharmacists was taken after completion of the upper-division classes in summer and fall 2001 and completed her university education. Dorothea Sauer worked 6 months of her 12 months required rotations in a public pharmacy (Berlin, Germany). She spent the remaining 6 months as visiting scientist at the University of Texas at Austin College of Pharmacy under the supervision of Dr. James W. McGinity. She collaborated with Weijia Zheng and investigated the aqueous coating of pellets with polymer blends. After completion of the rotations, she took the third German licensure examination for pharmacists in June 2003 and was awarded the German pharmacist license. In August 2003 she joined the University of Texas College of Pharmacy Ph.D. program under the direction of Dr. James W. McGinity. Dorothea Sauer worked as graduate research assistant and teaching assistant at the university. Her research focused on dry-powder coating of tablets and she attended various national and international meetings to present her work.

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Publications

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